2020-09-09

# Effectiveness of non-pharmacological interventions to treat orthostatic hypotension in elderly people and people with a neurological condition

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10.11124/jbisrir-d-18-00005
JBI Evidence Synthesis
Ovid Technologies (Wolters Kluwer Health)

# Effectiveness of non-pharmacological interventions to treat orthostatic hypotension in elderly people and people with a neurological condition: a systematic review

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## Abstract

**Objective**: The objective of this review was to summarize the best available evidence regarding the effectiveness of non-pharmacological interventions to treat orthostatic hypotension (OH) in elderly people and people with a neurological condition.

**Introduction**: Orthostatic hypotension is common in elderly people and people with a neurological condition and can interfere with or limit rehabilitation. Non-pharmacological interventions to treat OH could allow for longer and earlier mobilization, which is recommended in national clinical guidelines for rehabilitation in the acute or sub-acute phase following stroke or other neurological conditions.

**Inclusion criteria**: The review considered people aged 50 years and older, and people aged 18 years and elderly people with a neurological condition. Non-pharmacological interventions to treat OH included compression garments, neuromuscular stimulation, physical counter-maneuvers, aerobic or resistance exercises, sleeping with head tilted up, increasing fluid and salt intake, and timing and size of meals. The comparator was usual care, no intervention, pharmacological interventions, or other non-pharmacological interventions. Outcome measures included systolic blood pressure, diastolic blood pressure, heart rate, cerebral blood flow, observed/perceived symptoms, duration of standing or sitting in minutes, tolerance of therapy, functional ability, and adverse events/effects.

**Methods**: Databases for published and unpublished studies available in English up to April 2018 with no lower date limit were searched. Critical appraisal was conducted using standardized instruments from JBI. Data were extracted using standardized tools designed for quantitative studies. Where appropriate, studies were included in a meta-analysis; otherwise, data were presented in a narrative form due to heterogeneity.

**Results**: Forty-three studies—a combination of randomized controlled trials (n=13), quasi-experimental (n=28), case control (n=1), and case report (n=1)—were included. A total of 1084 participants met the criteria for inclusion. Meta-analysis was conducted for seven studies, which concluded that electrical stimulation, lower limb compression, and resistance exercise training were favorable in treating or reducing OH. However, the 95% confidence intervals for standardized mean difference crossed zero, and the confidence intervals in resistance exercise training were wide. Physical maneuvers such as leg crossing, leg muscle pumping/contractions, and bending forward improved orthostatic hypotension. Abdominal compression improved OH. Sleeping with head up in combination with pharmacological treatment was more effective than sleeping with head up alone. Eating smaller, more frequent meals was effective. Drinking 480 mL of water increased blood pressure.

**Conclusions**: The review found mixed results for the effectiveness of non-pharmacological interventions to treat OH in people aged 50 years and older, and people with a neurological condition. There are several non-pharmacological interventions effective in treating OH, but not all have resulted in clinically meaningful changes in outcome. Some may not be suitable for people with moderate to

severe disability; therefore, it is important for clinicians to consider the patient's abilities and impairments when considering which non-pharmacological interventions to implement.

**Key words**: Elderly, older adults; neurological condition; non-pharmacological treatment; orthostatic hypotension

***JBI Evid Synth. 2020;18(4):??-??***

## Summary of Findings

| **Resistance exercise compared to usual care for treating orthostatic hypotension in elderly people and people with a neurological condition** | | | | |
|---|---|---|---|---|
| **Bibliography:** Effectiveness of non-pharmacological interventions to treat orthostatic hypotension in elderly people and people with a neurological condition: a systematic review. JBI Evid Synth. 2020;18(4):??-??. | | | | |
| **Outcomes** | **№ of participants (studies) Follow-up** | **Certainty of the evidence (GRADE)** | **Anticipated absolute effects** | |
| | | | **Risk with usual care** | **Risk difference with resistance exercise** |
| Change in systolic blood pressure from supine to one-minute standing or 60 degrees head-up tilt<br>Change in systolic blood pressure assessed with mmHg<br>Follow-up: range 8 weeks to 12 weeks | 148<br>(1 RCT, 2 experimental) | ⨁◯◯◯<br>VERY LOW [a,b,c] | - | SMD **0.86 SD lower**<br>(CI: 2.34 lower to 0.63 higher) |
| CI: confidence interval; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference | | | | |
| **GRADE Working Group grades of evidence**<br>**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect<br>**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different<br>**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect<br>**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect<br>*Explanations*<br>a. Before and after study, non-blinded, or blinding of investigators not reported.<br>b. Variation in intervention: supervised sessions in Brilla; training performed four days per week in Zion, three days per week in Brilla, twice a week in Kanegusuku.<br>c. Small sample size in Zion, one-third of which were withdrawn during the intervention phase. | | | | |

**Electrical stimulation compared to usual care for treating orthostatic hypotension in elderly people and people with a neurological condition**

**Bibliography:** Effectiveness of non-pharmacological interventions to treat orthostatic hypotension in elderly people and people with a neurological condition: a systematic review. JBI Evid Synth. 2020;18(4):??-??.

| Outcomes | № of participants (studies) Follow-up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with usual care | Risk difference with electrical stimulation |
| Change in mean arterial blood pressure when moving from supine to one-minute standing or a vertical position on a tilt table following electrical stimulation compared with no intervention, robotic stepping, and electrical stimulation combined with robotic stepping compared with no intervention (change in mean arterial blood pressure when moving from supine to one-minute standing or a vertical position on a tilt table (MAP change))<br>assessed with: mmHg | 268<br>(2 observational studies) | ⨁◯◯◯<br>VERY LOW [a,b,c] | - | - | SMD **0.24 SD lower** (0.54 lower to 0.07 higher) |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; SD: standard deviation; SMD: standardized mean difference

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

*Explanations*

a. Observational study. No allocation concealment in Kuznetsov, participants randomized on day of admission
b. Heterogeneity in population, (e.g. stroke or spinal cord injury) and length of intervention (up to 30 days in Kuznetsov versus all testing on one-day Yoshida)
c. Yoshida made conclusions based on muscle strength and cerebral blood flow, they did not make any conclusions about effect of intervention on orthostatic reactions, yet this was one of their objectives.

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**Compression bandaging compared to usual care for treating orthostatic hypotension in elderly people and people with a neurological condition**

**Bibliography:** Effectiveness of non-pharmacological interventions to treat orthostatic hypotension in elderly people and people with a neurological condition: a systematic review. JBI Evid Synth. 2020;18(4):??-??.

| Outcomes | № of participants (studies) Follow-up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with usual care | Risk difference with compression bandaging |
| Change in mean arterial blood pressure when moving from supine to one-minute in sitting following compression bandaging compared with no intervention (Change in mean arterial blood pressure from supine to one-minute in sitting (MAP change)) assessed with: mmHg | 252 (2 observational studies) | ⨁◯◯◯ VERY LOW [a,b,c] | - | - | SMD **0.16 SD lower** (0.41 lower to 0.09 higher) |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; SD: standard deviation; SMD: standardized mean difference

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

*Explanations*
a. Observational study (residual confounding, evidence)
b. Before and after study, long-term effects not investigated. Study investigated seating induced orthostatic hypotension and did not measure effects in standing
c. Lead author and multiple co-authors were the same in both papers.

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## Introduction <level 1 heading>

Orthostatic (postural) hypotension (OH) is a common clinical phenomenon in elderly people and people with a neurological condition.[1-4] The consensus definition is a sustained drop of at least 20 mmHg in systolic blood pressure (sBP) and/or at least 10 mmHg in diastolic blood pressure (dBP) within three minutes of moving from supine to standing, or following head-up tilt to at least 60 degrees.[5,6]

Orthostatic hypotension has both non-neurogenic and neurogenic causes and can be acute or chronic.[6] Non-neurogenic causes fall into three categories: hypovolemia (reduced blood volume), cardiac pump failure, and venous pooling. Neurogenic OH is associated with neurological diseases and can be caused by abnormalities in either the central nervous system (e.g. stroke, spinal cord injury, Parkinson's disease) or peripheral nervous system (e.g. Guillain Barré syndrome, diabetic neuropathy)[7].

Orthostatic hypotension can cause a variety of symptoms and is a common cause of syncope (transient loss of consciousness, rapid onset, and short duration) that may contribute to morbidity, disability, and even death because of the potential risk of substantial injury.[5] Other characteristic symptoms include dizziness/light-headedness and pre-syncope; weakness, fatigue, and lethargy; palpitations and sweating; visual disturbances (including blurring, enhanced brightness, and tunnel vision); hearing disturbances (including impaired hearing, crackles, and tinnitus); and neck pain (occipital/para-cervical and shoulder region), low back pain, or precordial pain.[8,9] These symptoms relate to the degree of the fall in blood pressure and hypoperfusion (reduced blood flow) of the brain and other organs, and can vary in severity.

The prevalence of OH in elderly people (defined for this review as age 50 years and older[10]) is high, both in the United Kingdom (UK) and internationally, but varies depending on the characteristics of the population studied. It is more prevalent in elderly people who are hospitalized and institutionalized (up to 68%)[11] than in those living in the community (30%),[12] likely a reflection of the multiple disease processes, including neurological and cardiac conditions, as well as the type and number of prescribed medications. In addition, orthostatic changes in BP become more exaggerated after prolonged immobilization.[13] The prevalence of OH in people with neurological conditions is also high. Systematic reviews have concluded that OH occurs in approximately 40% of people with Parkinson's disease[2] and 50% to 82% of people with spinal cord injury, depending on the level of lesion.[3] It is also common in people with stroke,[1414] occurring in up to 52%.[4] Given that stroke predominantly occurs in elderly people, it is possible that the prevalence of OH post-stroke may be much higher. This aligns with current European guidelines, which highlight that OH is underdiagnosed.[5]

The presence of OH can interfere with and limit rehabilitation, especially after stroke and spinal cord injury where early mobilization (out-of-bed activities such as sitting, standing, and walking within 48

hours) is recommended.[15-18] Early mobilization has demonstrated improved functional outcomes[17]; however, studies of early mobilization in people with acute stroke excluded participants from the intervention arm if they had OH on three consecutive occasions.[18,19] Given the high incidence of OH in this population, this exclusion criterion could impact recruitment rates and generalizability of the findings of trials of early mobilization interventions, and ultimately influence the number of people potentially benefitting from these interventions.

The risk of harm with OH must be acknowledged and addressed. In acute and sub-acute stroke, OH has the potential to cause additional brain damage both in the area surrounding the stroke (penumbra) and throughout the brain due to hypoperfusion, a consequence of impaired cerebral autoregulation.[20] This may result in increased disability and mortality. Considering this risk of harm, it is surprising that current guidelines for the management of people with stroke[15,21,22] do not provide guidance on managing OH.

The goal of managing OH is to increase the patient's standing BP without also increasing their resting BP and specifically to reduce OH symptoms, increase the time the patient can stand, and improve the patient's ability to perform activities of daily living.[23] Currently, there is no specific intervention that achieves all of these goals, despite the multitude of pharmacological and non-pharmacological interventions available. A recent systematic review highlighted that although there were multiple pharmacological interventions available in the UK, Europe, and the United States of America (USA), there are few high-quality data as to which intervention the best.[24] Furthermore, the review concluded that there are limited data on the benefits of long-term pharmacological interventions in people with OH in terms of the effects on postural BP changes as well as symptom relief. The burden of pharmacological interventions also warrants consideration. People with stroke and elderly people are more likely to have multimorbidity[25] and thus are at risk of polypharmacy (taking five medications or more).[26] Therefore, identifying non-pharmacological interventions to treat OH in elderly people and people with stroke is paramount.

Reviews[27] and guidelines[5,28] from the USA and Europe for the management of OH recommend non-pharmacological interventions as first-line treatment before progressing to pharmacological interventions. However, people with neurological conditions often have complex needs and severe disability, which means that some non-pharmacological interventions may not be appropriate. For example, undertaking physical maneuvers requires a specific level of mobility and balance, and functional electrical simulation may be contraindicated due to other medical conditions or skin frailty. Therefore, these guideline recommendations cannot be automatically translated to people with neurological conditions, which underpins the rationale for this review. Non-pharmacological interventions for OH, such as compression garments, are used to treat OH in elderly people and those with spinal cord injury and Parkinson's disease,[29,30] and could be applicable to people with stroke. However, non-pharmacological interventions are not commonly used, and there is a lack of clear guidance on their use. In line with this, previous reviews of standing in people with neurological

conditions[31] have highlighted this as a research priority for people with OH, for elderly people, and adults with a neurological disease.[32]

An initial search of the literature in MEDLINE, Embase, CINAHL, Cochrane Database of Systematic Reviews, and PROSPERO identified one systematic review from Canada examining studies that evaluated non-pharmacological interventions to treat OH.[33] However, this review was broad, covering various patient populations and not restricted to elderly people or people with a neurological condition. Furthermore, the review did not focus on any specific outcomes, such as impact on mobilization or functional ability, thus identifying the need for a systematic review in this area. This review, together with a systematic review of pharmacological interventions,[24] will allow the development of a protocol to enable the assessment and treatment of OH in elderly people and people with neurological conditions.

# Review question <level 1 heading>

What is the evidence base for non-pharmacological interventions in treating orthostatic hypotension (OH) in elderly people and people with a neurological condition?

## Review objectives

The objectives of the review are to determine the effectiveness of non-pharmacological interventions for OH in elderly people and people with a neurological condition.

# Inclusion criteria <level 1 heading>

## Participants <level 2 heading>

The current review considered studies that included participants who were:

- Diagnosed with OH by a medical professional using criteria such as the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10)[34]
  AND
- Classified as elderly (defined as 50 years or over). Currently, there is no consensus definition of "elderly," ''older,'' or ''old people,'' with 50 years accepted as the definition of elderly people based on the World Health Organization Older Adult Health and Ageing in Africa project[10]
  AND/OR
- Aged 18 years and over with progressive or sudden, non-progressive neurological condition of the central nervous system; peripheral nervous system conditions were excluded.

Participants receiving treatment for acute or chronic OH were included, which encompassed treatment carried out in hospitals, outpatient clinics, in-patient rehabilitation units, and the community (either in their own homes, or in a residential or nursing home setting).

## Interventions <level 2 heading>

The review considered studies that evaluated non-pharmacological interventions to treat OH. These included compression garments (e.g. lower limb compression stockings or abdominal corset); neuromuscular stimulation; physical maneuvers (e.g. squatting and bending at the waist) and isometric exercises (muscle contractions against a resistant that are not associated with any movement of the limb) for arms, lower limbs, and abdominal muscles during standing; raising the head of bed at night time; or increasing fluid and salt intake. However, a full systematic search identified additional interventions that were considered (e.g. frequency and size of meals). Interventions of any duration, frequency, or intensity were considered.

## Comparators <level 2 heading>

The review considered studies that compared the non-pharmacological interventions listed previously with usual care, no intervention, pharmacological interventions, and/or other non-pharmacological interventions.

## Outcomes <level 2 heading>

Outcomes considered included sBP and/or dBP (both sBP and/or dBP in lying and standing using manual or automated device); time to symptoms and time to recovery; resting heart rate (HR) using manual or automatic device; cerebral blood flow using transcranial Doppler or correlation spectroscopy and others; observed and/or perceived symptoms; duration of standing or sitting in minutes; tolerance of therapy (e.g. ability to participate in therapy as measured by length and frequency of sessions); function/activities of daily living; other outcomes not previously identified; and adverse events/effects where this information was provided.

## Types of studies <level 2 heading>

This review considered experimental and epidemiological study designs including randomized controlled trials (RCTs), non-RCTs, quasi-experimental, before and after studies, prospective and retrospective cohort studies, and case-control studies. In addition, descriptive epidemiological study designs, including case series, and individual case reports were also considered.

# Methods <level 1 heading>

This systematic review was conducted in accordance with the JBI methodology for systematic reviews of effectiveness[35] and according to an *a priori* protocol (PROSPERO CRD42020167022).[36]

## Search strategy <level 2 heading>

The initial search was carried out in January 2017 and updated in April 2018, and aimed to find both published and unpublished studies. A three-step search strategy was utilized. An initial limited search of MEDLINE, AMED, CINAHL, and Embase was undertaken, followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the articles. A second search using all identified keywords and index terms was then undertaken across all included databases. Third, the reference lists of all studies that met the inclusion criteria were searched for additional studies. The search was restricted to studies published in English, as team members were unable to translate other languages. There were no date limits.

Information sources **<level 3 heading>**

Databases that were searched included MEDLINE (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials, CINAHL, AMED (EBSCO), PEDro, ClinicalTrials.gov, and OpenGrey. A search for unpublished studies was carried out in Google Scholar and Conference Papers Index. Appendix I provides the search strategy from all databases.

## Study selection <level 2 heading>

Following the search, all identified citations were uploaded into EndNote X8 (Clarivate Analytics, PA, USA) bibliographic software[37] and duplicates removed. Titles and abstracts were screened by two independent reviewers for assessment against the inclusion criteria for the review. The full text of potentially eligible studies was retrieved and assessed in detail against the inclusion criteria by two independent reviewers. The details of studies that met the inclusion criteria were imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia).[38] Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer.

## Assessment of methodological quality <level 2 heading>

Selected studies were critically appraised by two independent reviewers for methodological quality using the standardized critical appraisal instruments from JBI for the following study types: randomized controlled trials, quasi-experimental studies, case control studies, and case reports.[39] Disagreements were resolved through discussions, negating the requirement for a third reviewer. In

accordance with the aim to be as comprehensive as possible, all studies meeting the inclusion criteria were included in the review, regardless of the quality score.

## Data extraction <level 2 heading>

Quantitative data were extracted from papers using the standardized data extraction tool available in JBI SUMARI[39] by two independent reviewers (AL, JM, JP, JF, SB, and EC). The data extracted included specific details about the interventions, populations, study methods, outcomes of significance, and specific objectives.

Authors of papers were contacted to request missing or additional data where required. Thirteen authors were contacted, and responses were received from five.

## Data synthesis <level 2 heading>

Due to the variability and heterogeneity in the parameters of the papers presented, it was not possible to include all papers in the meta-analyses. For papers not included in the meta-analyses, data are presented as mean +/- standard deviation (SD) unless otherwise stated, alongside the narrative summary.

Outcomes for papers included in the meta-analyses were as follows: the change in mean arterial BP between supine and maximum upright stand or tilt (depending on what the studies measured) at the earliest measurement point (e.g. selecting measurements at one minute rather than two minutes, if both available). Where mean arterial pressure was not available, it was calculated with constant proportions between dBP and sBP: mean arterial pressure = 1/3 sBP + 2/3 dBP (mmHg).[40] Where dBP data were not available, the change in sBP was used.

Results, where possible, were pooled in statistical meta-analysis using JBI SUMARI. Effect sizes were expressed as standardized mean differences and their 95% confidence intervals calculated for analysis. Treatment effects were interpreted using Hedge's G magnitude of the standardized mean difference[41]. Standardized mean difference takes into account measurement variability, unlike the mean difference. Mean difference has greater statistical power and can be used if the minimally important change (MIC) is known[42]. However, there is no MIC for OH and the standardized mean difference is more therefore felt to be generalizable[42]. Heterogeneity was assessed statistically using the standard chi-squared and $I^2$ tests. The choice of random effects model and methods for meta-analysis were based on the guidance by Tufanaru et al.[43] There were insufficient individualized data to conduct subgroup analyses,[39] and insufficient number of studies to generate a funnel plot.[44]

## Assessing certainty in the findings <level 2 heading>

A Summary of Findings was created using GRADEpro software (McMaster University, ON, Canada) for all studies included in the meta-analysis. The GRADE approach for grading the quality of evidence was followed.[45] The Summary of Findings presents the following information, where appropriate: absolute risks for treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on study limitations (risk of bias), indirectness, inconsistency, imprecision, and publication bias.[45-48] The following outcomes were considered critical and were included in the Summary of Findings: mean arterial blood pressure and systolic blood pressure.

# Results <level 1 heading>

### Study inclusion <level 2 heading>

The results of the search and study selection process are presented in Figure 1.[49] A total of 4481 potentially relevant studies were identified. Table 5 shows the total number of relevant studies identified for each database. Of those, 1080 were duplicates. From the remaining 3401 records, 3316 were excluded after title and abstract assessment. The eligibility of 85 full-text articles were assessed, 42 of which were excluded. The methodological quality of the remaining 43 studies were assessed, which included 13 randomized control trials, 28 quasi-experimental studies, one case-control study and one case report.

<Insert Figure 1 here> Reference for PRISMA[50]

## Methodological quality <level 2 heading>

Methodological quality in all studies varied, but were included to provide a comprehensive review.

Table 1 presents the critical appraisal of the 13 RCTs included in the systematic review. True randomization was not used in one study, unclear in six studies, and used in six studies (Q1). Concealed allocation to treatment was used in five studies and unclear in four studies (Q2). Quality criteria relating to blinding of participants, clinicians, and researchers scored poorly in most studies (Q4 and Q5). Follow-up was either complete, or strategies to address incomplete follow-up were utilized in nine studies (Q8), and nine studies analyzed participants in the groups to which they were randomized (Q9).<Insert Table 1 here>

Table 2 presents the results of the critical appraisal for eligible quasi-experimental studies. Cause and effect was clear in all but one study (Q1). In five studies, Q2 and Q3 were not applicable because there were no comparisons made. There was no control group in nine of the 28 studies (Q4). Question 7 was deemed not applicable to one study because no comparisons were made.

<Insert Table 2 here>

Confounding factors were not identified (Q6) and no strategies to deal with confounding factors were present (Q7) in the case-control study. All other aspects of methodological quality were met (Table 3).<Insert Table 3 here>

Table 4 presents the critical appraisal results for the eligible case report. The post-intervention clinical condition was not clearly described (Q5), but all other aspects of methodological quality were reported.

<Insert Table 4 here>

## Characteristics of included studies <level 2 heading>

Date of publication of studies ranged from 1984 to 2018, and all were published in English. In the following sections, the main features of these studies are summarized. Detailed information about the settings, participants, methods, interventions, outcomes, and results are provided in Appendix II.

### Study settings <level 3 heading>

Twenty of the included studies were undertaken in Europe (four in United Kingdom[51-54], one in Ireland[55], six in the Netherlands,[56-61] three in Italy,[62-64] two in Germany,[65,66] one in Austria,[67] one in France,[68] and two in Switzerland[69,70]. Of the remaining 22 studies, 10 were undertaken in the USA,[71-80], three in Israel,[81-83] two in Canada,[84,85] two in Brazil,[86,87] one in India,[88] one in Malaysia,[89] one in Russia,[90] one in New Zealand,[91] and one in Australia[92] and it was unclear in which country one study was undertaken.[93] The interventions described were undertaken in hospital settings,[53,54,61,63,69,70,78,81-83,92] rehabilitation facilities,[62,64,65,68,76,77,88-90] outpatient clinics or centers,[51,55,58,71,75,85,86]

laboratories,[52,56,57,59,60,66,72,79,84,91], or community settings.[67,73,74,80,87] It was unclear which setting on study was conducted in[93].

### Participants <level 3 heading>

The 43 studies analyzed included a total of 1,069 participants, ranging from one (case report study[61]) to 128 (quasi-experimental study[90]). The age range of all participants was reported in 20 studies[51,53,56-61,67-69,72,75,76,79,80,84,85,89,92] and was from 18 to 89 years. Twenty-two studies[52,54,55,62-65,70,71,73,74,77,78,81-83,86-88,90,91,93] reported mean age. One study reported the age range for participants with autonomic failure and the mean age for nine participants with idiopathic OH.[66] There was a total of 440 elderly (≥50 years) participants.

Approximately 48% of all participants were male. Six studies included only males,[61,68,76,78,89,91] 16 studies included more males than females,[51,53,58,64,65,67,69,72,77,79,84,85,87,88,92,93] two studies had an equal number of males and females,[54,59] two studies reported the gender of participants with OH/neurological conditions but did not report gender for control participants.[60,71]

Studies in this systematic review included participants with OH (n=362), stroke (n=170), spinal cord injury (n=86), Parkinson's disease (n=57), brain injury (n=28), brain hemorrhage (n=18), syncope (n=21), familial dysautonomia (n=17), primary autonomic/autonomic failure (n=52), multi-system atrophy (n=31), cardiac arrhythmias (n=10), dizziness/palpitations (n=27), infectious diseases (n=21), pulmonary edema (n=10), acute coronary syndrome (n=11), decompensated heart failure (n=18), other conditions (n=39), and also healthy control participants (n=91). Four of the 1,069 participants had both spinal cord injury and OH, and others had multiple conditions.

Inclusion criteria for studies varied. Fourteen studies had OH as an inclusion criterion with a specific definition: 10 studies defined OH as a decrease in sBP of >20mmHg or a decrease in dBP >10mmHg after a change in posture.[55,62,67,74,80-83,88,89] Other definitions were a decrease in sBP >30mmHg or a decrease in dBP >15mmHg[72]; sBP decrease by at least 40mmHg or dBP decrease by at least 30mmHg[93]; a decrease in sBP of >30mmHg or a decrease in dBP >20mmHg[75], and progressive decrease in BP below a value of 90mmHg.[63] Eleven studies had OH as an inclusion criterion but did not provide a definition of OH.[51-54,56-60,66,73,] Nine studies had an age inclusion criterion of elderly people: ≥50 years,[87] ≥60 years,[55,80,82,83] or ≥65 years[62,70,81] or specified an age range[74] (60 to 85 years) Nineteen studies had neurological conditions as an inclusion criterion.[61,64,65,67-72,76-78,84,85,87-90,92]

### Interventions/comparators <level 3 heading>

Eight non-pharmacological interventions for OH were identified under two general categories: physical modalities (exercise, electrical stimulation, compression, physical counter-maneuvers, compression and physical counter-maneuvers, and sleeping with head up) and dietary measures (food and fluid intake), which aim to treat OH by raising standing blood pressure without raising supine blood pressure to increase the time people can stand and improve their ability to perform activities of daily living.

# Review findings <level 2 heading>

## *Physical modalities <level 3 heading>*

**Exercise**

Exercise included aerobic training using a cycle ergometer, resistance/strength training using resistance bands or weights, passive stepping using robotic tilt tables, and upper limb exercises. Nine studies included in this systematic review evaluated the effects of exercise on OH. Participants included in these studies had spinal cord injury,[78] brain injury,[62,64,65,69,74,80,86,87] brain haemorrhage,[69] stroke,[69] neurocardiogenic syncope,[86] Parkinson's disease,[87] and OH.[62,74,8062,88,90]

Four studies[64,65,78,86] used tilt tables, three of which[64,65,86] used robotic tilt tables where participants with brain injury undertook passive stepping while being tilted up to 65 degrees[64,65] and 70 degrees.[86] Duration of intervention periods were different: two sessions of sequential testing[65] (intended duration of testing in minutes not reported) and 24 sessions, each 30 minutes, three times per week.[64] The fourth study[78] used a tilt table and included participants with spinal cord injury who performed upper limb exercises while being tilted up to 70 degrees.

The effect of aerobic physical training was used in one study[86] for participants with neuro-cardiogenic syncope. Participants undertook a 12-week supervised program of moderate aerobic intensity training using a cycle ergometer. Training took place twice a week and lasted for 35 minutes, and patients were instructed to perform two additional unsupervised sessions.

One study[69] examined the effect of passive stepping at 30, 50, and 70 degrees using a robotic tilt table, automated cycling in supine versus standard care (defined as mobilization with physiotherapist), for patients with severe brain injury.

Four studies[62,74,80,87] examined the effects of resistance training on elderly people with OH. In one study,[62] participants performed 10 full extensions of the ankle, knee, and hip joints of both limbs starting from 60 degrees flexion of hips and 90 degrees flexion of knee and ankle joints against a resistance band (6-kg load) that participants positioned under the soles of their forefeet and firmly held at both ends while supine in bed prior to standing up. Participants in the three remaining studies[74,80,87] undertook a home-based resistance program, which incorporated exercises for both upper and lower limbs. These three studies were included in a meta-analysis (Figures 2, 3, and 4).[78]

Six studies[62,64,69,78,86,87,] in the exercise category had a control group, which consisted of tilting only,[62,64,78] standard care,[69,87] and stretching and light walking.[86] In one study[65] participants acted as their own controls in a randomized crossover design. Two studies included in the meta-analysis (Figure 2) did not include a control group.[74,8062,88]

<Insert Figure 2 here>

**Electrical stimulation**

Electrical stimulation is a technique that uses low energy electrical pulses to artificially generate a muscle contraction of paralyzed muscles. When used in a functional context to elicit patterns of movement, it is also referred to as functional electrical stimulation. The studies included in this review used electrical stimulation of upper limbs, lower limbs, and abdomen.

Seven studies examined the effects of electrical stimulation on OH.[71,76,77,84,85,89,90] Participants in one study[90] had a stroke; the other six studies included people with spinal cord injury. Two papers[71,77] reporting on the same study included the same sample and examined the same experimental interventions, differing slightly in the measured outcomes. They compared upright stationary standing versus upright dynamic standing using functional electrical stimulation, both using a standing apparatus for 30 minutes on the same day. Another repeated measures study[76] positioned participants in multiple tilt angles (0, 15, 30, 45, and 60 degrees), four minutes at each angle followed by four minutes recovery, repeated with and without electrical stimulation to the lower limb (bilateral knee extensors and ankle plantar flexor muscles). One study[89] included two participants who underwent four weeks of electrical stimulation to trunk and lower-limb muscles (rectus abdominis, quadriceps, hamstrings, and gastrocnemius muscles), four times per week for one hour per day. One study[84] tested the capacity of electrical stimulation, applied transcutaneously over the spinal cord (approximately corresponding to the T8 spinal segment) to manage OH in participants with spinal cord injury. Two studies[85,90] used a robotic tilt table and electrical stimulation to compare passive stepping and passive stepping combined with electrical stimulation. These were included in a meta-analysis (Figure 3).

<Insert Figure 3 here>

Use of control group varied: three studies included a control group,[48,65,71] two studies[55,68] had no control group, and participants acted as their own controls in one study.[64,86]

**Compression**

Compression involves using various types of bandages and garments on different body parts, commonly the lower limbs and abdomen. Fourteen studies[51,57,61,63,67,68,72,75,81-83,88,91,92] examined the effect of compression on OH. Participants were elderly with OH,[51,63,72,81-83] had acute stroke,[88] Parkinson's disease,[67] neurogenic OH,[75,63], autonomic dysfunction,[57], healthy older and younger adults[91] spinal cord injury.[61,68,92]

Two studies,[63,88] both RCTs, examined the effect of compression to both the abdomen and lower limbs. In one study,[63] elderly participants with OH wore ankle to thigh bandages for 10 minutes, then an abdominal bandage was added for a further 10 minutes. Participants then wore leggings, which covered from the mid foot to the abdomen, for one month at home. Authors reported that these were worn daily but did not report any recommendations or report usage from follow-up data. In the other

study,[88] participants with acute stroke wore a pneumatic abdominal binder and pneumatic calf compression for six consecutive sessions for approximately 15 minutes during progressive incline on a tilt table.

Four studies[57,67,72,92] examined the effect of abdominal compression on OH. Participants with Parkinson's disease[67] were enrolled into a randomized crossover trial. They wore an abdominal binder or placebo binder. Participants then wore an abdominal binder every day (time not specified) for four weeks. The second study,[72] a randomized crossover trial, assessed the effects of a conventional or patient-controlled adjustable abdominal binder on OH. Binders were worn for approximately 10 minutes during the testing period. The third study[57] tested the effect of abdominal compression (maximal pressure protocol 1 and graded compression protocol 2) of participants with autonomic dysfunction. The fourth study[92] enrolled participants with spinal cord injury into a randomized crossover trial. Participants wore an abdominal binder (pressure not reported) daily (time not specified) for six months.

Three studies examined the effect of lower limb compression during tilt tabling,[51,61,75] all of which used different compression garments and different pressures on different body parts. In one study,[75] participants with neurogenic OH underwent tilt testing with and without compression applied to calves, thighs, and abdomen using an inflatable G-suit to evaluate the impact of compression of different body parts on orthostatic BP and tolerance. Another study,[61] a case report, tested one participant with spinal cord injury on a tilt table with and without inflatable external leg compression to bilateral lower limbs. The third study[51] tested elastic compression hosiery (tights covering the legs and abdomen) fitted to bilateral lower limbs in elderly participants.

One study[68] examined the effects of a wheelchair ergometer with and without graduated compression stockings. Participants with spinal cord injury used the wheelchair ergometer twice: once with garment compression stockings and once without a week later. Additional details are presented in Appendix II.

One study[91] examined the effect of compression leggings at normal body temperature and a long-sleeved and legged, two piece, tube-lined perfusion suit at elevated body temperature in healthy elderly people and younger adults.

Three studies[81-83] examined the effect of lower limb compression bandages from ankle to thigh on OH. All three studies included elderly participants who were hospitalized due to acute medical conditions,[81] decompensated heart failure,[82] and OH.[83] In all three studies, compression bandages were applied along both legs from ankle to thigh before sitting without compression and repeated with compression. In one study,[81] compression was approximately 30mmHg at the ankle. The remaining two studies used 40mmHg compression[82] and 30-40mmHg compression[83] at the ankle. The latter two studies were included in a meta-analysis (Figure 4).

<Insert Figure 4 here>

In 10 studies, participants acted as their own controls,[51,57,67,68,72,75,81-83,910] two studies had a control group,[63,88] and two studies had no control group.[61,92]

**Physical counter-maneuvers**

Physical counter-maneuvers are specific movements or exercises such as squatting, leg crossing, or tensing specific muscles with the aim of increasing standing BP and reducing OH. Five studies[56,58,60,73,93] were identified in the literature search that examined the effect of physical counter-maneuvers on OH, varying in the number and type of maneuvers performed. Participants in these studies had OH due to pure autonomic failure,[56,58,60] neurogenic OH,[73] and familial dyautomonia.[93]

One study[73] examined the use of multiple physical counter-maneuvers for three to four months following a training period. Training consisted of four training sessions in the laboratory performing the physical counter-maneuvers. Participants were then asked to perform the three selected maneuvers at home for three to four months when symptomatic.

In one study,[60] all participants performed leg-crossing and squatting in a fixed order. Participants stood for 10 minutes maximum or until symptoms occurred, then performed leg-crossing in standing for 30 seconds then resumed normal standing. When BP dropped again, participants squatted for 30 seconds then resumed the normal standing position.

In one study,[56] participants performed nine different maneuvers, each for one minute serially, separated by 30 to 60 seconds of standing. Participants were asked to sit on seats of varying heights (48 cm, 38 cm, 20 cm), with or without leg-crossing, squatting, and standing in a crossed-leg position with or without additional contraction of the lower limb muscles. All maneuvers were repeated twice and performed in a random order.

One study[93] examined the effect of four physical counter-maneuvers (bending forward, squatting, and leg crossing in a random order) in 17 participants with familial dysautonomia. Participants also completed a fourth physical counter-maneuver using abdominal compression.

One study[58] compared leg muscle pumping or tensing for one minute, commencing after two minutes of active standing, compared to active standing only.

Three studies did not include a control group,[56,73,93] and two studies included a control group.[58,60]

**Physical counter-maneuvers and compression**

Two studies used a combination of physical counter-maneuvers and compression. One study[5780] examined the effects of abdominal compression and physical maneuvers in participants with neurogenic hypotension. Participants maintained a standing position with the abdominal binder and then performed physical maneuvers in standing while wearing an anti-gravity suit. For nine

participants, the duration of standing was extended (duration not specified) by standing without crossed legs or abdominal compression. As soon as a stable low BP was obtained for 30 seconds, the counter-maneuvers were repeated for 90 seconds, followed by a short period of normal standing. Nine participants (unclear if it was the same nine who undertook extended standing) performed two active standing maneuvers; external abdominal compression was applied by elastic binder.

Another study[93] compared the effect of physical counter-maneuvers, one of which was abdominal compression. Participants performed four counter-maneuvers (bending forward, squatting, leg crossing, abdominal compression) in a randomized order and abdominal compression using an inflatable belt. Outcomes were measured before and after

**Sleeping head-up tilt**

One study[55] examined the effect of sleeping with the head of the bed elevated by six inches for six weeks. The control group received no intervention. Another study[59] examined the effect of sleeping with the head of bed elevated with and without pharmacological intervention and 2,000mL water per day. There was no control group, but there was a control period during the first week.

## *Dietary measures <level 3 heading>*

**Food intake**

Studies in this category examined the size and frequency of meals and their effect on OH. Three studies[53,70,79] examined the effect of food intake on OH.

One study[70] tested participants with Parkinson's disease and 10 age-matched controls over two consecutive days to examine the change in sBP induced by meals. They also compared the impact of orthostatic sBP response in participants with Parkinson's disease with that of control participants.

One study[79] examined the effect of meal size and the time of day on OH in elderly and young healthy participants.

The final study[53] examined the effect of meal size and number of meals in people with autonomic failure. All participants underwent the same conditions: the first day participants ate three meals versus the second day (at least one day apart) when participants ate six meals. Total calorie intake was the same over both days.

Participants acted as their own controls in two studies,[53,70] and one study did not include a control group.[79]

**Fluid intake**

Ingesting water to increase BP and attenuate OH was examined in three studies.[52,54,66] Participants in all three studies drank 480 mL of fluid; however, additional variables such as food intake and exercise were also studied.

One study[52] examined the effect of ingesting water before exercise on OH. All participants had severe pre-exercise OH and underwent the same testing using a cycle ergometer. Testing was undertaken on two separate occasions, one in which participants drank 480 mL distilled water.

A second study[66] examined the effect of water ingestion and food intake. All participants underwent two protocols. In protocol 1, participants drank 480 mL of tap water; in protocol 2, participants drank 480mL of water immediately before eating the test meal.

The final study[54] in the category examined the effects of drinking 480 mL distilled water. All participants had autonomic failure and underwent the same testing: standing BP was measured before, and 15 and 35 minutes after ingesting of 480 mL distilled water.

Two studies[52,66] did not include a control group, and in the third study[87] participants acted as their own controls.

## Follow-up and measurement intervals <level 2 heading>

Follow-up periods varied: 30 days,[71] one month,[56] four weeks,[50,68] eight weeks,[62,88,59] 12 weeks,[52,58] three to four months,[61] and 14 months.[81]

## Outcomes <level 2 heading>

A wide variety of outcome measures were used in the included studies. Several outcomes included in this review were not identified a priori and have been highlighted in the limitations section. The most common objective outcomes were sBP and/or dBP, (used in all 43 studies) and HR,[52-59,61-66,68-75,78-81,84,86-93] cardiac output,[52,54-58,68,71,75,77,91,93] and stroke volume.[52,54-58,61,68,71,77,84,85,90,91,93]. Other objective outcomes included the following: total peripheral resistance,[52,54-57,71,77,91,93] mean arterial pressure,[55,71,77,84,89,91-93] mean BP,[56,58-60,67,69,73,85,93] oxygen saturations,[61,81,82] respiratory rate,[69] resistance index,[73,90] HR variability,[68] stroke index,[73] cardiac index,[61,73,75] maximum power output,[68] maximum systolic velocity,[90] minimum diastolic velocity,[90] end diastolic index,[73] peripheral resistance index,[75] end diastolic volume index,[75] pulsatility index,[90] systemic vascular resistance,[58] inferior caval vein,[57] femoral vein,[57] rate pressure product,[77] perfusion index,[61] cerebral blood flow,[69,90] blood velocity of middle and posterior cerebral artery,[84] cerebral vascular resistance,[91] calf impedence,[93] electrocardiographic RR-intervals,[87,93] Valsalva maneuvers,[66,87] hyperventilation test,[66] cold pressor test,[52,66] oxygen uptake,[68] end-tidal partial pressure of carbon dioxide,[91] peak expiratory flow,[92] forced expiratory flow,[92] forced vital capacity,[92] voice measures,[92] interruption of verticalization,[65] maximal cardiopulmonary exercise test,[86] fluid balance,[55,59] esophageal temperature,[91] venous blood and plasma samples,[69] and edema.[5549]

Observed or perceived orthostatic symptoms were measured using a variety of methods. The most common method was self-report,[53-56,59,60,76,81-83,85,89] where participants described their symptoms. One study[84] asked participants to rank their symptoms from one to 10. Other studies used formal outcome measures: Specific Symptom Scale Questionnaire for Orthostatic Intolerance,[63] global symptomatic improvement score,[73] Orthostatic Symptom Scale,[72] severity of OH symptoms,[75] orthostatic tolerance,[59] Symptom Change Scale,[72] Orthostatic Hypotension Questionnaire,[67] OH Daily Activity Scale,[67] and OH Symptom Assessment.[67]

Two studies measured maximum standing time.[52,59] Three studies used measures of disability and function: Timed Up and Go Test,[80] Barthel Index[90] and modified Rankin Scale.[88] Other measures were measures of muscle strength,[52,66,80,87,90] one repetition maximum,[74,87] and electromyography of leg muscles.[85]

### *Physical modalities <level 3 heading>*

**Exercise interventions** delivered during tilt tabling demonstrated mixed results. Greater tolerance of verticality and reduced occurrence of OH was observed in three studies.[64,65,78] Passive stepping using robotic tilt tables was effective at reducing the number of OH symptoms,[64,65] and this was also observed when performing upper limb exercises during verticalization.[78] A 12-week aerobic training program[86] resulted in an increase in orthostatic tolerance and reduction of positive head-up tilt tests. Lower limb resistance exercises[62] were the least effective, resulting in minimal reduction in an initial fall in sBP when moving from supine to standing. No significant absolute or relative difference was observed in any of the BP components with passive cycling or passive stepping.[69] However, there was a higher difference in arterial BP in both the intervention groups compared with standard physiotherapy. Three studies[74,80,87] investigating the effects of resistance exercise training were included in a meta-analysis (Figure 2), which concluded that resistance exercise training was favorable compared to no intervention. A large mean effect size of -0.86 was observed favouring the intervention however the 95% confidence intervals for the standardized mean difference crossed zero and were wide (-2.34-+0.63). Figure 2 also shows show significant heterogeneity ($P$<0.0001) of studies.

*Conclusion of effectiveness*: Exercise interventions may improve orthostatic tolerance, but there were no statistically significant results with any of the exercise interventions.

**Electrical stimulation** was favorable but not statistically significant in the five studies not included in the meta-analysis. In these studies, participants using electrical stimulation could stand for longer and had reductions in OH,[71,77] demonstrated a longer tolerance time during head-up tilt,[89] and had normalized BP.[76,84] The overall outcome of the two studies[85,90] included in the meta-analysis (Figure 3) showed that a combination electrical stimulation and robotic stepping was more effective than robotic stepping only or control.

*Conclusion of effectiveness*: Results for the studies not included in the meta-analysis favored the intervention of electrical stimulation, but were not statistically significant. A comparison of robotic stepping and electrical stimulation (ROBO-FES) with robotic stepping (ROBO) showed a small effect size (-0.32) favouring ROBO-FES but with 95% CI that cross zero (-0.80 to 0.17). A comparison of robotic stepping and electrical stimulation (ROBO-FES) with control showed a small effect size (-0.44) favouring ROBO-FES but with 95% CI that cross zero (-0.92 to 0.04).**Compression** demonstrated positive results for elderly people with OH and people with neurogenic OH. Two studies[63,88] concluded that combined lower limb and abdominal compression improved orthostatic stability in elderly people and people with stroke.

Abdominal compression[57,67,72] was shown to reduce OH in elderly people with neurogenic OH. Abdominal compression significantly reduced BP fall upon tilting[67] compared to placebo. Symptoms of OH decreased significantly at the four-week follow-up. Abdominal compression was effective at attenuating OH compared with no abdominal compression,[72] and symptoms were not affected by type of binder. There was no statistically significant difference with or without abdominal binder[92]; however, mean arterial BP was higher with the abdominal binder at six weeks and at six months.

Three lower limb compression studies reported positive results. Maximum improvement was observed with all three combinations of compression (calves, thighs and abdomen),[75] and abdominal compression alone significantly reduced OH ($P$<0.005). Similarly, a significant improvement was observed in elderly people with OH wearing elastic hosiery tights,[51] with a reduction of OH at one minute ($P$<0.01) and at two minutes ($P$<0.005). The spinal cord injury case report[61] demonstrated that the individual was able to remain in the upright position for longer, allowing improved mobilization during physiotherapy while wearing the inflatable external leg compression. The inflatable external leg compression succeeded in improving pre-syncope symptoms and preventing OH for several hours.

Participants with spinal cord injury demonstrated an increase in sympathetic activity and a decrease in parasympathetic activity after maximal exercise while wearing graduated compression stockings using the wheelchair cycle ergometer.[68]

Lower limb compression stockings[91] caused a passive physical resistance that, upon standing, delayed the maximal drop in mean arterial pressure in both younger adults and elderly people. The authors of the study concluded that compression stockings appeared to reduce venous pooling; however, the total peripheral resistance increased in elderly participants in minute 6. There were no differences between groups when heat and orthostatic stress were combined.

Lower limb compression bandages[81] decreased OH symptoms in participants who were medically unwell, including 14 with stroke. Approximately 55% of participants experienced symptoms in the un-bandaged group. Significant changes were observed in the un-bandaged group compared to the bandaged group, with significantly greater incidence of palpitations, tachycardia, and decline of oxygen saturation over time ($P$<0.04, $P$<0.03, $P$<0.03, respectively). The authors did not report results for sBP or dBP. Results from the two studies[82,83] included in the meta-analysis (Figure 4) favor

compression bandaging, but the effect size was small and the 95% confidence interval cross zero (-0.16 95% CI -0.41 to 0.09).

*Conclusion of the effectiveness*: Lower limb and abdominal compression,[51,63,88] lower limb compression,[51,61,68,81-83,91] and abdominal compression[57,67,72,92] are effective in improving OH; however, not all studies were statistically significant.

**Physical counter-maneuvers** were deemed effective in reducing OH in people with neurogenic OH, if performed correctly.[73] Squatting produced the most dramatic change in arterial BP, resulting in longer standing time improved. The follow-up survey identified that the use of the maneuvers varied from once to 11 times per day (3.83 ±3.1 maneuvers per day). However, the follow-up survey was conducted via telephone; therefore, it was unknown whether participants were performing maneuvers correctly.

Leg crossing and squatting[60] improved standing BP in people with autonomic failure. After leg crossing, all participants stood for 10 minutes or more (pre-intervention standing times not provided). Time in standing after squatting was not reported.

Leg crossing and leg muscle contractions[56] resulted in higher standing BP than without leg muscle contraction. Leg crossing while sitting on 48-cm and 38-cm chairs demonstrated an increase in sitting BP in people with pure autonomic failure.

Leg muscle pumping (tiptoeing and leg crossing)[58] had different effects on OH in people with autonomic failure. Tiptoeing did not change BP after one minute in the patient group, but the normative group showed an increase in BP. Leg-crossing increased BP in both groups initially, which was more pronounced in the normative group.

Physical maneuvres[93] that significantly increased mean BP included bending forward ($P$<0.005), squatting ($P$<0.002), and abdominal compression ($P$<0.04) but not leg crossing. Squatting and abdominal compression also induced a significant increase in cardiac output during squatting ($P$<0.02) and during abdominal compression ($P$<0.014).

*Conclusion of effectiveness: Physical counter-maneuvers,*[60,73,93] leg crossing,[56,60,93] leg muscle pumping/contractions,[56] squatting and bending forward[93] improved OH, while tiptoeing did not.[58] Leg crossing while sitting on 48-cm and 38-cm chairs demonstrated an increase in sitting BP.[56]

**A combination of abdominal compression and physical counter-manouvres** had a significant effect on standing BP in one study ($P$<0.05[57]) and significant increase in cardiac output in another study ($P$=0.02[72]). However, there were no significant differences in the effect of abdominal compression on the diameter of caval or femoral veins, or compression and arterial pressure response.[57]

*Conclusion of the effectiveness:* A combination of abdominal compression and physical counter-maneuvers is effective in treating OH.

**Sleeping with head up** reduced BP after one minute of standing (*P*<0.01 for sBP).[59] Four of the six participants adopted this intervention. Combined treatment (sleeping with head up and pharmacological treatment using fludrocortisone) was most effective, significantly reducing OH symptoms in all patients (*P*<0.001) and increasing the maximal standing period to at least 10 minutes compared to 35 to 170 seconds pre-treatment. Sleeping with head up at six inches for six weeks had no effect on OH symptoms and BP.[55]

*Conclusion of the effectiveness*: Sleeping with head up in combination with fludrocortisone was more effective than sleeping with head up alone.

### *Dietary measures <level 3 heading>*

**Food intake** had a negative effect on BP in elderly people and people with neurogenic OH. Participants with Parkinson's disease had a significant (*P*<0.01) postprandial sBP drop in supine position compared to healthy controls.[70] There was a greater fall in sBP with passive versus active standing in both groups, with a greater postprandial fall in the group with Parkinson's disease. The authors reviewed one meal (lunch) and did not look at all meals throughout an entire day or collect data on the size of meals participants usually ate with those provided in the study.

Post-meal BP was lower in all positions[53] (lying sBP *P*<0.005, lying dBP *P*<0.02, sitting dBP *P*<0.07, standing dBP *P*<0.06) after three large meals. Compared to six meals, sBP and dBP between meals reached lower levels on the three-meal study day. Fewer symptoms were reported during the six-meal study day.

Post-meal supine BP was significantly lower (*P*<0.02) in elderly participants.[79] Supine sBP and dBP were significantly higher (*P*<0.15 and *P*<0.001) in the elderly group, but standing sBP and dBP were similar between groups.

*Conclusion of effectiveness*: Eating smaller, more frequent meals as opposed to larger, less frequent meals resulted in significantly higher supine, sitting, and standing BP and improved OH symptoms in people with autonomic failure, people with neurogenic OH, elderly people, and people with Parkinson's disease.

**Fluid intake** prior to standing had a positive effect on OH in various positions. Five minutes after drinking water, there was a significant rise in BP in the supine position (*P*<0.05).[52] With exercise there was a clear fall in BP, which occurred even after water ingestion. Blood pressure remained low after exercise but was significantly higher (*P*<0.05) after water intake, resulting in better tolerance of post-exercise standing. Drinking water improved orthostatic tolerance post-exercise. Standing prior to water ingestion caused a significant fall (*P*<0.01) in BP in all participants.[66] After water ingestion, there was a rise in seated BP. Seated and standing BP at 15 and 35 minutes after water ingestion was significantly higher (*P*<0.01 and *P*<0.001) than before water, with an improvement in orthostatic symptoms.

Drinking 480 mL of water at room temperature in less than five minutes improved standing BP and orthostatic tolerance in people with autonomic failure.[54] The response was similar in patients with

multiple system atrophy and those with pure autonomic failure. Water ingested before a meal attenuated postprandial hypotension in these patients. Drinking water also attenuated orthostatic tachycardia in people with idiopathic orthostatic intolerance.

*Conclusion of effectiveness*: Ingestion of water increased BP in supine,[70] sitting,[78] and standing.[78,87] Water ingested prior to a meal also attenuated postprandial hypotension.[87]

## Discussion <level 1 heading>

This review set out to examine the effectiveness of non-pharmacological interventions to treat OH in elderly people and people with a neurological condition.

Although the literature contained many non-pharmacological interventions to treat OH in these populations, the review highlighted a heterogeneity of methods. The inclusion criteria included some participants who did not have a formal diagnosis of OH prior to entering a study. Many studies included participants with neurological conditions such as Parkinson's disease, brain injury, stroke and spinal cord injury, but did not specify OH as an inclusion criterion. This may be because OH in neurological conditions is associated with central autonomic dysfunction or the absence of vein blood pump related to lower limb paralysis. Additionally, periods of immobility or prolonged bed rest, which can cause physiological changes such as diminished sympathetic activity,[94] in combination with hypovolemia, may also predispose some individuals with neurological conditions to OH. However, authors did not explicitly provide this as a rationale for their chosen sample.

Thirty-one percent of studies specified OH in their inclusion criteria, but there was heterogeneity in the definitions used, and only 26% provided a definition, which makes meaningful comparison difficult. The most commonly used definition was a sustained drop in sBP of at least 20 mmHg and/or dBP of at least 10 mmHg following a change of posture, which was applied to various postures (standing, tilting [ranging from 15 to 90 degrees tilt angles], or sitting). Other variations used a higher threshold.[72,75,93] Using higher thresholds could result in participants being missed during screening. It also raises the question as to whether the lack of standardization observed in these studies is mirrored in clinical practice. The time points at which BP was measured also varied from immediately[62,63] to up to 10 minutes[74,90] of being upright. Further, the definition of "being upright" varied from 60 to 90 degrees on a tilt table or self-initiated standing, and authors did not acknowledge or discuss the differences between active and passive standing. Verticalization using a tilt table does not fully replicate the physiology of active standing because the exercise reflex and the mechanical squeeze on the venous capacitance and arterial resistance vessels are less.[95] Therefore, OH may occur more frequently with tilt-table testing.[96]

Cerebral hypoperfusion is acknowledged in clinical guidelines[5,28] as a common cause of syncope or transient loss of consciousness,[97] which is likely to impact standing time and symptoms experienced. Monitoring cerebral blood flow is important in people with acute or sub-acute stroke, because autoregulation is impaired following stroke.[20] Two recent meta-analyses[98,99] concluded that OH was independently associated with a significantly higher risk of developing coronary heart disease,

cardiovascular disease, and heart failure. Despite the relative importance of maintaining cerebral blood flow when standing upright, it was measured in only two studies. One study[69] monitored cerebral blood flow, but only in participants with sub-arachnoid hemorrhage and not in participants with ischemic stroke or severe brain trauma. The authors acknowledged the potential risk of impairing cerebral blood flow during mobilization but did not provide a rationale for only monitoring participants with sub-arachnoid hemorrhage. Additionally, they did not provide any data on cerebral blood flow. The second study[90] included 104 participants with stroke (128 recruited but 28 dropped out), all of whom had cerebral blood flow measured pre- and post-training. Cerebral blood flow was reduced ≤10%, but participants were asymptomatic. Asymptomatic OH is more common than symptomatic OH,[100] which means clinicians may be unaware of the potential risk of further brain damage when these patients are being mobilized or undergoing therapy. As well as measuring cerebral blood flow, future work should investigate what is a clinically important drop in cerebral blood flow.

**Which interventions worked? <level 2 heading>**

Overall, the results were mixed. Although effect sizes often favored the intervention in individual studies, meta-analyses of three interventions were statistically non-significant. The mean effect sizes were either large (resistance exercise) or small (electrical stimulator or compression bandaging) and in all cases the95% confidence intervals for the standardized mean difference crossed the line of no effect as highlighted in the forest plots in Figures 2, 3, and 4. In general the sample sizes were small and although there were differences seen these are small and this has potentially been influenced by the small sample sizes. Of the additional interventions reviewed, physical counter-maneuvers and fluid intake produced favorable results. It is important to consider the feasibility and practicality of these interventions if they are to be implemented into clinical practice.

Physical counter-maneuvers were favorable in reducing OH, for example, but people with balance and mobility problems may find many of the physical maneuvers challenging, and their risk of falling increased. Additionally, performing these physical maneuvers requires the ability to stand and move between sitting and standing, and people with moderate and severe disability would often not be able to perform these movements without mechanical or physical assistance. Exercise was favorable, but the changes measured were not statistically significant. The resistance training programs may also be unsuitable for people with moderate to severe disability. Several studies used robotic tilt tables and automated cycle ergometers to passively move lower limbs during verticalization, which may be more suitable for people with neurological conditions who have moderate to severe disability. When considering implementation into practice, it is important to consider how accessible this equipment is; robotic tilt tables, for instance, are not routinely available in clinical practice.

Other interventions that may be suitable for people with moderate to severe disability are compression and electrical stimulation. Compression garments, such as compression stockings, may allow repeated safe standing or sitting. They can be used in conjunction with tilt tables and standing frames to facilitate orthostatic tolerance, and are commonly used in spinal cord rehabilitation.[101] In stroke, current clinical guidelines recommend intermittent pneumatic compression or graded

777 compression stockings of lower limbs as thromboembolism prophylaxis.[102] Therefore, abdominal
778 binders may be more appropriate as they would not interfere with this. Furthermore, abdominal
779 binders may be easier for healthcare providers to monitor skin integrity, and they provide less risk of
780 skin damage. However, abdominal binders are contraindicated for people receiving nutritional support
781 via a gastrostomy tube, because the binder would compress the tube and may cause pain and skin
782 damage. Additionally, people with moderate to severe disability may need assistance to don and doff
783 compression garments.

784 Electrical stimulation is an adjunctive intervention commonly used in clinical practice to treat muscle
785 impairment.[103] Contraindications for electrical stimulation include poor skin integrity, significant
786 autonomic dysreflexia in incomplete spinal cord injury above T6, and uncontrolled epilepsy.[104] Only
787 one study provided this information.[89] None of the studies discussed the contraindications of using
788 electrical stimulation in clinical practice. However, contractions induced by electrical stimulation of
789 lower limb muscles may activate the skeletal muscle pump as effectively as voluntary contractions of
790 these muscles in people without weakness or disability as a result of stroke or neurological
791 impairment. This may allow patients to stand earlier or for longer during rehabilitation sessions or
792 performing activities of daily living. The two studies included in the meta-analysis investigating the
793 effectiveness of electrical stimulation versus control had small sample sizes and within these there
794 were significant variability. Although the studies indicate a better absolute effect using electrical
795 stimulation, this is not reflected in the meta-analysis. This is due to the variability and the small
796 sample size.

797 Water ingestion had a positive effect on OH and would be suitable for many people. However, stroke
798 and degenerative neurological conditions can cause swallow impairments[105]; therefore, ingesting
799 water quickly may be unsafe or challenging for these people due to risk of aspiration and aspiration
800 pneumonia. Further, people who have incontinence or reduced mobility that affects their ability to get
801 to the toilet may be reluctant to undertake this intervention. This intervention would also be unsuitable
802 for people who have fluid restriction due to other medical conditions. All three studies tested water
803 ingestion on a one-off basis making the accumulative effects unknown.

804 Long-term follow-up and prolonged intervention regimes were lacking in most studies. Therefore, it is
805 unknown whether OH improves over time with repeated application of a specific non-pharmacological
806 intervention and whether improvements are sustained, alleviating the need for further intervention
807 over the longer term. None of the studies evaluated instantaneous versus training effects (e.g.
808 repeated interventions) of the different OH interventions. For example, an abdominal binder improved
809 OH when it was worn for four weeks,[67] but because there was no follow-up beyond this point, it was
810 not known if symptoms returned once it was no longer worn. This warrants different trial designs with
811 longer follow-up periods.

812 Determining long-term effects is important because studies suggest the cardiovascular system can
813 adapt over time to develop orthostatic tolerance. In spinal cord injury, for example, these adaptations
814 may be due to changes in Rennin–angiotensin–aldosterone activity.[106,107] Further, adaptations in the

central control of autonomic functions have been identified in healthy animals with prolonged exercise training and may occur over time and with training in people with OH.[108]

There may be a difference in the short- and long-term effects of the interventions between conditions. Where there is direct damage to autonomic centers, such as in multiple system atrophy[109] and Parkinson's disease,[110] the potential for adaptive changes may be limited. In contrast, there may be greater potential for central and neuro-hormonal adaptive changes in the elderly and in people after stroke, where causes may be more linked to paralysis and long-term immobility. This highlights the need for future studies to stratify participants according to both their condition and stage or severity of disease. Different conditions have different pathophysiological mechanisms underlying OH[111-113] and thus potentially different short- and long-term effects of an intervention.

**Limitations <level 2 heading>**

The primary limitation of this review was the heterogeneity of methods of the studies included.

Significant variability between studies Most studies had small sample sizes, which limits generalizability of the results. The methodological quality of the included studies varied. For RCTs, randomization was not used or unclear, and blinding in most RCTs was low. Some quasi-experimental studies did not include a comparator or control group. The number of participants included in the meta-analyses varied: electrical stimulation (n=38[90] and n=10[85]), compression (n=53[82] and n=73[83]), and exercise (n=53[74]; n=14[87]; n=8[80]). The certainty of the evidence was very low for all studies included in the meta-analysis, thus any translation into practice must be tentative. Subgroup analysis was not possible due to insufficient number of studies included in the meta-analysis, as well as inconsistency of reported demographics, medications, and severity of neurological condition using disease-specific validated outcome measures.

Outcomes not previously identified in the protocol development were identified through this systematic review process, and the authors recognize this as a protocol deviation: cardiac output,[52,54-58,68,71,75,77,91,93] and stroke volume.[52,54-58,61,68,71,77,84,85,90,91,93]. Other objective outcomes included the following: total peripheral resistance,[52,54-57,71,77,91,93] mean arterial pressure,[55,71,77,84,89,91-93] mean BP,[56,58-60,67,69,73,85,93] oxygen saturations,[61,81,82] respiratory rate,[69] resistance index,[73,90] HR variability,[68] stroke index,[73] cardiac index,[61,73,75] maximum power output,[68] maximum systolic velocity,[90] minimum diastolic velocity,[90] end diastolic index,[73] peripheral resistance index,[75] end diastolic volume index,[75] pulsatility index,[90] systemic vascular resistance,[58] inferior caval vein,[57] femoral vein,[57] rate pressure product,[77] perfusion index,[61] cerebral blood flow,[69,90] blood velocity of middle and posterior cerebral artery,[84] cerebral vascular resistance,[91] calf impedence,[93] electrocardiographic RR-intervals,[87,93] Valsalva maneuvers,[66,87] hyperventilation test,[66] cold pressor test,[52,66] oxygen uptake,[68] end-tidal partial pressure of carbon dioxide,[91] peak expiratory flow,[92] forced expiratory flow,[92] forced vital capacity,[92] voice measures,[92] interruption of verticalization,[65] maximal cardiopulmonary exercise test,[86] fluid balance,[55,59] esophageal temperature,[91] venous blood and plasma samples,[69] and edema.[55]

This review was further limited by the inclusion of only English language studies.

## Conclusion <level 1 heading>

This review found mixed results for the effectiveness of non-pharmacological interventions to treat OH in people 50 years and older and people with a neurological condition. The settings, participants, outcomes, study designs, and intervention types were heterogeneous, resulting in an inability to include all studies in a meta-analysis. There are several non-pharmacological interventions that may be effective in treating OH (electrical stimulation, lower limb and abdominal compression, physical maneuvers, resistance exercise training, eating smaller and more frequent meals, and drinking 480 mL water), but not all have resulted in clinically meaningful changes in outcome. However, those studies included in the meta-analyses were non-significant, and the 95% confidence intervals for the standardized mean difference crossed the line of no effect and were wide. Sleeping with head up in combination with pharmacological treatment was more effective than sleeping with head up alone. Some interventions may not be suitable for people with moderate to severe disability (e.g. they may be unable to stand to perform physical maneuvers or perform resistance training due to weakness). Thus, it is important for clinicians to consider a patient's abilities and impairments when choosing which non-pharmacological interventions to implement.

### Recommendations for practice <level 2 heading>

The findings of this systematic review have several implications for clinicians working with people with neurological conditions and elderly people in both inpatient and community settings. Although not statistically significant, meta-analysis concluded that electrical stimulation, lower limb compression, and resistance exercise training were favorable in reducing OH, although the GRADE certainty of evidence was very low for all three physical modalities. These modalities could be implemented into rehabilitation sessions for people with stroke, people with neurological conditions, and elderly people.

Many rehabilitation units have cycle ergometers (e.g. MOTOmed, Thera Trainers), which patients could use while sitting out, even in specialist wheelchairs. However, depending on the severity of disability, some patients may need supervision to optimize safety. Additionally, many rehabilitation units also have access to functional electrical stimulation (e.g. Microstim), which could be incorporated into standing practice to increase the duration of standing and optimize physical activity during rehabilitation sessions. Clinicians need to check whether patients have any contraindications (e.g. spinal cord injury above T6, uncontrolled epilepsy, poor skin integrity, cognitive problems).

When OH is problematic, lower limb compression and abdominal binders could be used, both within and outside of rehabilitation sessions, to optimize physical activity. Abdominal binders are easier to don and doff than lower limb compression stockings, making them easier for patients to use independently. For those who require assistance with compression, education of clinicians, carers, and family members is required so that patients can use them within and outside of rehabilitation sessions, and in the community setting.

The applicability of water ingestion for people with neurological conditions has been acknowledged. If patients have been screened by speech and language therapists and deemed to have no swallow impairment, sipping water may be a useful way of managing OH during standing practice.

This review suggests a range of non-pharmacological interventions may be effective in managing OH. Most do not require specialist equipment and training; therefore, the cost of implementation is likely to be minimal. Importantly, from a practical perspective, many of these interventions can be implemented inside or outside of rehabilitation sessions. However, the patient's physical abilities and impairments (e.g. cognitive impairment, severity of disability, swallow impairment) should be considered when selecting a non-pharmacological intervention.

**Recommendations for future research <level 2 heading>**

This systematic review highlighted heterogeneity in measurement of non-pharmacological interventions to treat OH. Lack of a standardized approach to measurement in OH trials makes consolidation of the body of knowledge difficult, which may negatively impact on effective interventions being implemented into clinical practice. A consensus is required when measuring BP at specific time points during standing or verticalization. Further, a consensus is required for measuring OH in people with neurological conditions who have impaired mobility and reduced standing times. Additionally, a core set of outcome measures and standardized time points would facilitate pooling of results in meta-analyses to enable more accurate conclusions to be drawn.

Standardization of inclusion criteria is required to ensure that all participants enrolled in OH intervention studies have OH, either by testing during screening or from a formal diagnosis. Improved consistency of methodology reporting, as recommended by the Consolidated Standards of Reporting Trials guidelines,[122] is also recommended. Consistency of reporting demographics, medications, and severity of neurological condition using disease-specific validated outcome measures would allow subgroup analysis.

## Funding

This systematic review presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

## Conflicts of interest

The authors declare no conflict of interest.

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# Appendix I: Search strategy

Each of the databases listed below were searched individually as part of one search in January 2017. The search was repeated on April 26 and 27, 2018 to update the search prior to submission for publication. Limiters for all searches: English language. The number of relevant studies identified in each database is shown in Table 5. The number of records identified (number of hits for each search formula) for each database is shown in the results column on the right-hand side of each table. Advice was sought from an information scientist and guidance given to report it in the following ways:

**MEDLINE (Ovid)**

| Search ID # | Search formula | Records retrieved |
|---|---|---|
| S1 | orthostatic adj2 hypotension AB | 641 |
| S2 | hypotension, orthostatic/ MeSH, AB | 843 |
| S3 | postural adj2 hypotension AB | 88 |
| S4 | orthostasis AB | 138 |
| S5 | dizziness/ MeSH AB | 2367 |
| S6 | “low blood pressure” AB | 322 |
| S7 | hypotension/ MeSH AB | 5181 |
| S8 | vascular adj2 response AB | 645 |
| S9 | “autonomic dysfunction” AB | 1519 |
| S10 | “cerebral blood flow” or “cerebral bloodflow” AB | 5119 |
| S11 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S9 OR S10 | 16,541 |
| S12 | Elder* OR “older people” OR “older person” OR aged/ OR ageing OR aging OR senior OR geriatric AB | 485,281 |
| S13 | S11 AND S12 | 2436 |
| S14 | "non-pharmacological treatment*" OR "nonpharmacological treatment*" OR "non pharmacological treatment*" AB | 455 |
| S15 | "non-pharmacological management" OR "nonpharmacological management" OR "non pharmacological management" AB | 79 |
| S16 | "non-pharmacological intervention*" OR "nonpharmacological intervention*" OR "non pharmacological intervention*" AB | 547 |
| S17 | 14 OR 15 OR 16 | 1081 |
| S18 | Physical AB | 218,418 |
| S19 | S13 AND S18 | 396 |
| S20 | S11 AND S12 AND S17 | 9 |
| S21 | S11 AND S17 | 19 |
| S22 | compression ajd2 garment* AB | 90 |
| S23 | compression adj2 stocking* AB | 411 |
| S24 | compression adj2 bandag* AB | 386 |

| | | |
|---|---|---|
| S25 | compression adj2 wrap* AB | 8 |
| S26 | stockings, compression/ AB | 321 |
| S27 | abdominal binder AB | 13 |
| S28 | S22 OR S23 OR S24 OR S25 OR S26 OR S27 | 1229 |
| S29 | S13 AND S28 | 11 |
| S30 | S11 AND S28 | 23 |
| S31 | S13 AND S17 | 8 |
| S32 | rehabilitation AB | 954 |
| S33 | S13 AND S32 | 0 |
| S34 | S11 AND S32 | 1 |
| S35 | exercise AB | 12,723 |
| S36 | S35 AND S11 | 56 |
| S37 | S11 AND “physical maneuvers” or “physical man*” or “physical measures” AB | 25 |
| S38 | diet AB and S11 | 0 |
| S39 | fluid AND S11 | 0 |
| S40 | water AND S11 | 0 |
| S41 | meals AND S11 | 0 |
| S42 | food AND S11 | 0 |
| S43 | vasovagal AND management OR treatment AB | 0 |
| S44 | S11 AND “head up” OR “head-up” AB | 16 |
| S45 | S11 and “electrical stimulation” AB | 2 |
| S47 | Parkinson* OR Alzheimer* OR dementia OR “multiple sclerosis” OR “motor neuron*” OR stroke AB | 188,454 |
| S47 | exp stroke/ MeSH AB | 25,475 |
| S48 | exp neurodegenerative disease*/ MeSH AB | 52,263 |
| S49 | exp dementia/ MeSH AB | 24,907 |
| S50 | exp multiple sclerosis/ MeSH AB | 16,962 |
| S51 | exp cerebrovascular disorder/ MeSH AB | 47,426 |
| S52 | exp brain ischemia/ MeSH AB | 19,725 |
| S53 | exp spinal cord injuries/ MeSH AB | 19,147 |
| S54 | exp brain injuries/ MeSH AB | 15,167 |
| S55 | craniocerebral trauma/ MeSH AB | 2014 |
| S56 | exp central nervous system disease/ MeSH AB | 197,427 |
| S57 | exp brain damage, chronic/ MeSH AB | 22,074 |
| S58 | Parkinson* adj2 disease AB | 20,277 |
| S59 | S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 | 197,363 |
| S60 | S11 AND S59 | 2689 |
| S61 | S11 AND S17 AND S59 | 8 |

| | | |
|---|---|---|
| S62 | S11 AND intervention OR treatment | 962 |
| S63 | S11 AND “functional electrical stimulation” OR FES OR “electrical stimulation” OR “neuromuscular stimulation” | 0 |

1214

1215 **CINAHL (EBSCO)**

| Search ID # | Search formula | Records retrieved |
|---|---|---|
| S1 | orthostatic adj2 hypotension AB | 745 |
| S2 | hypotension, orthostatic/ MeSH, AB | 1011 |
| S3 | postural adj2 hypotension AB | 163 |
| S4 | orthostasis AB | 89 |
| S5 | dizziness/ MeSH AB | 3615 |
| S6 | “low blood pressure” AB | 1220 |
| S7 | hypotension/ MeSH AB | 6579 |
| S8 | vascular adj2 response AB | 640 |
| S9 | “autonomic dysfunction” AB | 992 |
| S10 | “cerebral blood flow” or “cerebral bloodflow” AB | 2769 |
| S11 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S9 OR S10 | 11,975 |
| S12 | Elder* OR “older people” OR “older person” OR aged/ OR ageing OR aging OR senior OR geriatric AB | 770,143 |
| S13 | S11 AND S12 | 11,975 |
| S14 | "non-pharmacological treatment*" OR "nonpharmacological treatment*" OR "non pharmacological treatment*" AB | 586 |
| S15 | "non-pharmacological management" OR "nonpharmacological management" OR "non pharmacological management" AB | 160 |
| S16 | "non-pharmacological intervention*" OR "nonpharmacological intervention*" OR "non pharmacological intervention*" AB | 319 |
| S17 | 14 OR 15 OR 16 | 909 |
| S18 | Physical AB | 254,613 |
| S19 | S13 AND S18 | 399 |
| S20 | S11 AND S12 AND S17 | 7 |
| S21 | S11 AND S17 | 13 |
| S22 | compression ajd2 garment* AB | 2039 |
| S23 | compression adj2 stocking* AB | 411 |
| S24 | compression adj2 bandag* AB | 3136 |
| S25 | compression adj2 wrap* AB | 38 |
| S26 | stockings, compression/ AB | 411 |
| S27 | abdominal binder AB | 32 |
| S28 | S22 OR S23 OR S24 OR S25 OR S26 OR S27 | 4812 |
| S29 | S13 AND S28 | 14 |
| S30 | S11 AND S28 | 40 |

| | | |
|---|---|---|
| S31 | S13 AND S17 | 7 |
| S32 | rehabilitation AB | 83,688 |
| S33 | S13 AND S32 | 142 |
| S34 | S11 AND S32 | 3469 |
| S35 | exercise AB | 60,566 |
| S36 | S35 AND S11 | 9 |
| S37 | S11 AND “physical maneuvers” or “physical man*” or “physical measures” AB | 1 |
| S38 | diet AB and S11 | 2 |
| S39 | fluid AND S11 | 10 |
| S40 | water AND S11 | 4 |
| S41 | meals AND S11 | 1 |
| S42 | food AND S11 | 5 |
| S43 | vasovagal AND management OR treatment AB | 2 |
| S44 | S11 AND “head up” OR “head-up” AB | 1038 |
| S45 | S11 and “electrical stimulation” AB | 2130 |
| S47 | Parkinson* OR Alzheimer* OR dementia OR “multiple sclerosis” OR “motor neuron*” OR stroke AB | 67,201 |
| S47 | exp stroke/ MeSH AB | 29,841 |
| S48 | exp neurodegenerative disease*/ MeSH AB | 1208 |
| S49 | exp dementia/ MeSH AB | 15,734 |
| S50 | exp multiple sclerosis/ MeSH AB | 5738 |
| S51 | exp cerebrovascular disorder/ MeSH AB | 861 |
| S52 | exp brain ischemia/ MeSH AB | 478 |
| S53 | exp spinal cord injuries/ MeSH AB | 6811 |
| S54 | exp brain injuries/ MeSH AB | 9820 |
| S55 | craniocerebral trauma/ MeSH AB | 16 |
| S56 | exp central nervous system disease/ MeSH AB | 335 |
| S57 | exp brain damage, chronic/ MeSH AB | 465 |
| S58 | Parkinson* adj2 disease AB | 2403 |
| S59 | S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 | 731,686 |
| S60 | S11 AND S59 | 1054 |
| S61 | S11 AND S17 AND S59 | 1 |
| S62 | S11 AND intervention OR treatment | 1018 |
| S63 | S11 AND “functional electrical stimulation” OR FES OR “electrical stimulation” OR “neuromuscular stimulation” | 3 |

**Embase (Ovid)**

| Search ID # | Search formula | Records retrieved |
|---|---|---|
| S1 | orthostatic adj2 hypotension AB | 12,134 |
| S2 | hypotension, orthostatic/ MeSH, AB | 8751 |
| S3 | postural adj2 hypotension AB | 8453 |
| S4 | orthostasis AB | 1235 |
| S5 | dizziness/ MeSH AB | 59,620 |
| S6 | “low blood pressure” AB | 1999 |
| S7 | hypotension/ MeSH AB | 83,977 |
| S8 | vascular adj2 response AB | 4 |
| S9 | “autonomic dysfunction” AB | 13,763 |
| S10 | “cerebral blood flow” or “cerebral bloodflow” AB | 33,465 |
| S11 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S9 OR S10 | 193,841 |
| S12 | Elder* OR “older people” OR “older person” OR aged/ OR ageing OR aging OR senior OR geriatric AB | 2,361,227 |
| S13 | S11 AND S12 | 36,198 |
| S14 | "non-pharmacological treatment*" OR "nonpharmacological treatment*" OR "non pharmacological treatment*" AB | 4063 |
| S15 | "non-pharmacological management" OR "nonpharmacological management" OR "non pharmacological management" AB | 2120 |
| S16 | "non-pharmacological intervention*" OR "nonpharmacological intervention*" OR "non pharmacological intervention*" AB | 5964 |
| S17 | 14 OR 15 OR 16 | 4625 |
| S18 | Physical AB | 141,178 |
| S19 | S13 AND S18 | 179 |
| S20 | S11 AND S12 AND S17 | 44 |
| S21 | S11 AND S17 | 169 |
| S22 | compression ajd2 garment* AB | 2493 |
| S23 | compression adj2 stocking* AB | 3196 |
| S24 | compression adj2 bandag* AB | 2009 |
| S25 | compression adj2 wrap* AB | 2695 |
| S26 | stockings, compression/ AB | 1615 |
| S27 | abdominal binder AB | 138 |
| S28 | S22 OR S23 OR S24 OR S25 OR S26 OR S27 | 154,794 |
| S29 | S13 AND S28 | 1408 |
| S30 | S11 AND S28 | 5437 |
| S31 | S13 AND S17 | 44 |
| S32 | rehabilitation AB | 45,333 |
| S33 | S13 AND S32 | 108 |
| S34 | S11 AND S32 | 10,191 |
| S35 | exercise AB | 93,653 |

| | | |
|---|---|---|
| S36 | S35 AND S11 | 7912 |
| S37 | S11 AND “physical maneuvers” or “physical man*” or “physical measures” AB | 103 |
| S38 | diet AB and S11 | 65 |
| S39 | fluid AND S11 | 936 |
| S40 | water AND S11 | 140 |
| S41 | meals AND S11 | 1206 |
| S42 | food AND S11 | 1057 |
| S43 | vasovagal AND management OR treatment AB | |
| S44 | S11 AND “head up” OR “head-up” AB | 1040 |
| S45 | S11 and “electrical stimulation” AB | 2167 |
| S47 | Parkinson* OR Alzheimer* OR dementia OR “multiple sclerosis” OR “motor neuron*” OR stroke AB | 282,575 |
| S47 | exp stroke/ MeSH AB | 128,930 |
| S48 | exp neurodegenerative disease*/ MeSH AB | 14,461 |
| S49 | exp dementia/ MeSH AB | 82,503 |
| S50 | exp multiple sclerosis/ MeSH AB | 9104 |
| S51 | exp cerebrovascular disorder/ MeSH AB | 47,059 |
| S52 | exp brain ischemia/ MeSH AB | 8,9618 |
| S53 | exp spinal cord injuries/ MeSH AB | 46,684 |
| S54 | exp brain injuries/ MeSH AB | 105,520 |
| S55 | craniocerebral trauma/ MeSH AB | 11,371 |
| S56 | exp central nervous system disease/ MeSH AB | 19,412 |
| S57 | exp brain damage, chronic/ MeSH AB | 1562 |
| S58 | Parkinson* adj2 disease AB | 6701 |
| S59 | S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 | 705,295 |
| S60 | S11 AND S59 | 27,078 |
| S61 | S11 AND S17 AND S59 | 56 |
| S62 | S11 AND intervention OR treatment | 947 |
| S63 | S11 AND “functional electrical stimulation” OR FES OR “electrical stimulation” OR “neuromuscular stimulation” | 9 |

**AMED (EBSCO)**

| Search ID # | Search formula | Records retrieved |
|---|---|---|
| S1 | orthostatic adj2 hypotension AB | 43 |
| S2 | hypotension, orthostatic/ MeSH, AB | 42 |
| S3 | postural adj2 hypotension AB | 12 |
| S4 | orthostasis AB | 6 |

| | | |
|---|---|---|
| S5 | dizziness/ MeSH AB | 275 |
| S6 | “low blood pressure” AB | 28 |
| S7 | hypotension/ MeSH AB | 177 |
| S8 | vascular adj2 response AB | 36 |
| S9 | “autonomic dysfunction” AB | 78 |
| S10 | “cerebral blood flow” or “cerebral bloodflow” AB | 98 |
| S11 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S9 OR S10 | 666 |
| S12 | Elder* OR “older people” OR “older person” OR aged/ OR ageing OR aging OR senior OR geriatric AB | 15,557 |
| S13 | S11 AND S12 | 91 |
| S14 | "non-pharmacological treatment*" OR "nonpharmacological treatment*" OR "non pharmacological treatment*" AB | 73 |
| S15 | "non-pharmacological management" OR "nonpharmacological management" OR "non pharmacological management" AB | 16 |
| S16 | "non-pharmacological intervention*" OR "nonpharmacological intervention*" OR "non pharmacological intervention*" AB | 22 |
| S17 | 14 OR 15 OR 16 | 87 |
| S18 | Physical AB | 26,973 |
| S19 | S13 AND S18 | 28 |
| S20 | S11 AND S12 AND S17 | 0 |
| S21 | S11 AND S17 | 0 |
| S22 | compression ajd2 garment* AB | 26 |
| S23 | compression adj2 stocking* AB | 21 |
| S24 | compression adj2 bandag* AB | 20 |
| S25 | compression adj2 wrap* AB | 3 |
| S26 | stockings, compression/ AB | 26 |
| S27 | abdominal binder AB | 6 |
| S28 | S22 OR S23 OR S24 OR S25 OR S26 OR S27 | 76 |
| S29 | S13 AND S28 | 0 |
| S30 | S11 AND S28 | 0 |
| S31 | S13 AND S17 | 0 |
| S32 | rehabilitation AB | 40,721 |
| S33 | S13 AND S32 | 41 |
| S34 | S11 AND S32 | 5 |
| S35 | exercise AB | 16,599 |
| S36 | S35 AND S11 | 2 |
| S37 | S11 AND “physical maneuvers” or “physical man*” or “physical measures” AB | 0 |
| S38 | diet AB and S11 | 2 |
| S39 | fluid AND S11 | 0 |
| S40 | water AND S11 | 2 |

| | | |
|---|---|---|
| S41 | meals AND S11 | 0 |
| S42 | food AND S11 | 0 |
| S43 | vasovagal AND management OR treatment AB | 0 |
| S44 | S11 AND “head up” OR “head-up” AB | 0 |
| S45 | S11 and “electrical stimulation” AB | 5 |
| S47 | Parkinson* OR Alzheimer* OR dementia OR “multiple sclerosis” OR “motor neuron*” OR stroke AB | 9734 |
| S47 | exp stroke/ MeSH AB | 5851 |
| S48 | exp neurodegenerative disease*/ MeSH AB | 156 |
| S49 | exp dementia/ MeSH AB | 1699 |
| S50 | exp multiple sclerosis/ MeSH AB | 1204 |
| S51 | exp cerebrovascular disorder/ MeSH AB | 109 |
| S52 | exp brain ischemia/ MeSH AB | 40 |
| S53 | exp spinal cord injuries/ MeSH AB | 3294 |
| S54 | exp brain injuries/ MeSH AB | 3074 |
| S55 | craniocerebral trauma/ MeSH AB | 2 |
| S56 | exp central nervous system disease/ MeSH AB | 69 |
| S57 | exp brain damage, chronic/ MeSH AB | 12 |
| S58 | Parkinson* adj2 disease AB | 27 |
| S59 | S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 | 15,637 |
| S60 | S11 AND S59 | 163 |
| S61 | S11 AND S17 AND S59 | 0 |
| S62 | S11 AND intervention OR treatment | 14 |
| S63 | S11 AND “functional electrical stimulation” OR FES OR “electrical stimulation” OR “neuromuscular stimulation” | 0 |

**PEDro (Physiotherapy Evidence Database)**

| Search ID # | Search formula | Records retrieved |
|---|---|---|
| S1 | orthostatic adj2 hypotension | 19 |
| S2 | hypotension, orthostatic | 19 |
| S3 | postural adj2 hypotension | 6 |
| S4 | orthostasis | 2 |
| S5 | dizziness | 273 |
| S6 | “low blood pressure” | 413 |
| S7 | hypotension | 50 |
| S8 | vascular adj2 response | 53 |
| S9 | “autonomic dysfunction” | 36 |
| S10 | “cerebral blood flow” or “cerebral bloodflow” | 0 |

| | | |
|---|---|---|
| S11 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S9 OR S10 | 421 |
| S12 | Elder* OR “older people” OR “older person” OR aged/ OR ageing OR aging OR senior OR geriatric | |
| S13 | S11 AND S12 | |
| S14 | "non-pharmacological treatment*" OR "nonpharmacological treatment*" OR "non pharmacological treatment*" | 87 |
| S15 | "non-pharmacological management" OR "nonpharmacological management" OR "non pharmacological management" | 73 |
| S16 | "non-pharmacological intervention*" OR "nonpharmacological intervention*" OR "non pharmacological intervention*" | 94 |
| S17 | S14 OR S15 OR S16 | 315 |
| S18 | S11 AND S17 | 0 |
| S19 | S11 AND compression | 3 |
| S20 | S11 AND electrical stimulation | 4 |
| S21 | stroke OR neurodegenerative disease* OR dementia OR multiple sclerosis OR neurological OR Parkinson* OR motor neuron* | |
| S22 | S11 AND S21 | 2 |

**Cochrane Central Register of Controlled Trials**

| Search ID # | Search formula | Records retrieved |
|---|---|---|
| S1 | orthostatic adj2 hypotension: TI, AB, KW | 1287 |
| S2 | "non-pharmacological" OR "nonpharmacological" OR "non pharmacological” OR treatment OR intervention OR management: TI, AB, KW | 1751 |
| S3 | compression: TI, AB, KW | 5616 |
| S4 | S1 AND S2 | 22 |
| S5 | S4 AND S3 | 20 |

**Clinical Trials Register**

| Search formula | Records retrieved |
|---|---|
| (orthostatic hypotension OR orthostatic; hypotension, neurogenic OR orthostatic; hypotension, dysautonomia) AND (treatment OR intervention OR management): TI, AB, KW | 134 |

**OpenGrey**

| Search formula | Records retrieved |
|---|---|
| abstract: (orthostatic hypotension OR postural hypotension OR low blood pressure OR cerebral blood flow) AND abstract: (nonpharmacological OR non-pharmacological OR non pharmacological) AND abstract: (intervention OR treatment OR management) | 396 |

TI: Title; AB: Abstract; KW: keyword

# Appendix II: Characteristics of included studies

Eight non-pharmacological interventions for orthostatic hypotension were identified under two general categories: physical modalities (exercise, electrical stimulation, compression, compression and physical counter-maneuvers, physical counter-maneuvers, and sleeping with head up) and dietary measures (food and fluid intake).

## Physical modalities

### Exercise

| Study | Country and setting | Participant characteristics | Experimental intervention | Control intervention | Outcomes measured | Description of main results |
|---|---|---|---|---|---|---|
| Luther et al., 2008[65] Randomized crossover pilot trial using sequential testing | Germany, neuro-rehabilitation unit | N=9 unconscious within first three months of brain injury; (5 male)<br>Mean age: 51 (± 20) years | Tilt table with an integrated stepping device<br>Intervention and control delivered in a random order on different days one week between testing | Conventional tilt table | Primary: interruption of verticalization due to a syncope or presyncope symptoms such as tachypnea, tachycardia, pallor, or increase in sweating<br>Secondary: state of consciousness according to Coma Recovery Scale-Revised; influence of treatment on muscle tone using Modified Ashworth Scale | There were significantly more incidences of presyncope on the conventional tilt table ($P$<0.05) at tilts of 50 or 70 degrees compared to the tilt table with integrated stepping. The binominal test as a cross-check showed significantly more treatment discontinuations on the conventional tilt table than on the tilt table with integrated stepping ($P$=0.031). |
| Takahagi et al., 2014[86] | Brazil, outpatient | N=21 recurrent neuro-cardiogenic syncope with | N=11 undertook aerobic physical training using | N=10 undertook 15 minutes of stretching and | Resting and training HR, $VO_2$ peak, $VO_2$ anaerobic threshold, | The training group exhibited a tendency for higher peak HR, with $VO_2$ peak and $VO_2$ anaerobic |

| | | | | | | |
|---|---|---|---|---|---|---|
| Randomized controlled trial | | had positive head-up tilt test (3 male)<br>Mean age: 32 (±10) years in intervention group; 26 (±8) years in control group | cycle ergometer for 12 weeks<br>Two supervised sessions plus two unsupervised sessions | 15 minutes of light walking for 12 weeks<br>2 supervised sessions | sBP and dBP before and after 12-week training | threshold than the control group. The training group exhibited a statistically significant difference ($P$<0.01) in syncope episodes between pre- and post-intervention.<br>There was a significant difference ($P$<0.05) in the number of negative head-up tilt (72.7% in the training group versus 30% in the control group). |
| Taveggia et al., 2015[64]<br>Randomized controlled trial | Italy, neuro-rehabilitation unit | N=12 with vegetative state or minimally conscious state 3-18 months after acute acquired brain injury (8 male)<br>Mean age: 65 (±8) years in intervention group; 63 (±16) years in control group | N=6 tilted to 65 degrees with a robotic tilt table system performing 18 steps per minute of the lower limbs (hip and knee flexion) for 30 minutes three times a week for 24 sessions | N=6 tilted to 65 degrees for 30 minutes with no lower-limb movement | HR and BP monitored at every tilt angle<br>Coma recovery scale and level of consciousness scale pre- and post treatment; OH occurrence and length | n=4 withdrawn due to medical events.<br>Intervention group showed a progressive reduction in OH during treatment; n=3 showed a complete absence of OH at the end of rehabilitation therapy.<br>Control group showed more serious OH after 24 sessions of treatment.<br>BP readings not reported, but the group tilted with robotic stepping experienced less OH during verticalization (48 and 4 seconds) compared to the control group (120 and 187 seconds). |
| Rocca et al., 2016[69]<br>Randomized controlled trial | Switzerland, inpatient hospital | N=30 (n=14 sub-arachnoid hemorrhage; n=4 severe brain trauma; n=4 intra-parenchymal hemorrhage, n=2 ischemic stroke, n=3 brain anoxia, n=3 other (17 male)<br>Age range: 18-88 years<br>Mean age: 54.2 years | N=10 passive cycling in supine (protocol 2)<br>N=10 passive stepping with robotic tilt table (protocol 3) | N=10 standard physiotherapy (protocol 1) | sBP and dBP, HR, respiratory rate, cerebral blood flow for participants with sub-arachnoid hemorrhage, venous blood, and blood plasma samples | No significant absolute or relative difference in any of the BP components with passive cycling or passive stepping. |

| Study | Country and setting | Participant characteristics | Groups | Outcomes measured | Main description of results |
|---|---|---|---|---|---|
| Brilla et al., 1998[74]<br>Quasi-experimental | USA, community | N=24 elderly with OH (a subset of n=53 participants from a larger study on a high-resistance strength training in elderly people; all 24 showed orthostatic hypotension in the pre-test) (7 male)<br>Mean age: 71 (±5.8) years | All participants underwent 8 weeks heavy resistance, progressive strength training program, upper and lower limbs.<br>Participants were discontinued from the study if more than two consecutive sessions were missed. | i) Resting BP in supine, sitting, and standing positions<br>ii) Resting HR in supine, sitting, and standing positions<br>iii) Response to orthostatism in rising from supine after 10 minutes and rising from a chair after five minutes | Significant changes ($P$<0.05) in supine dBP (+3.2 mmHg), sitting systolic BP (-3.9 mmHg), and standing HR (+4.9 beats per minute). In response to orthostatic challenge, significant ($P$<0.05) improvements in sBP (+9.7 mmHg), dBP (+4.7 mmHg) and HR (+3.2 beats per minute) for the rise from chair, and in dBP (+6.7 mmHg) rise from cot. Gains in strength were also noted. |
| Zion et al., 2003[80]<br>Quasi-experimental | USA, community | N=12 orthostatic hypotension. Only 8 completed the protocol.<br>N=8 (4 male)<br>Age range: 63to 81 years | N=8 completed an 8-week home-based resistance-training program using elastic resistance bands. 10 exercises (incorporating upper and lower limbs) were assigned and customized to each participant. | Orthostatic testing: ECG and beat-to-beat BP continuously monitored and recorded.<br>BP in supine, seated, standing one minute, standing two minutes, and during tilt table testing weeks 1 and 8 at rest, 60-degree tilt, end tilt.<br>Muscle strength testing (isometric and dynamic)<br>Functional test of gait and mobility (Timed Up and Go Test) at baseline and 8 weeks | At 8 weeks, significant increases occurred in dynamic strength in the chest press ($P$<0.017), quadriceps extension ($P$<0.017), and leg press ($P$<0.025); no significant differences occurred in isometric strength or in BPs. Functional mobility increased in seven out of eight participants.<br>No falls during the investigation period. |

| Study | Country and setting | Participant characteristics | Experimental group | Control group | Outcomes measured | Main description of results |
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| Kanegusuku et al., 2017[87]<br>Randomized controlled trial | Brazil, community | N=30 Parkinson's disease and n=16 healthy controls (33 male)<br>Age range: 67 (± 8); (Parkinson's Disease Training Group) | Parkinson's disease progressive resistance training | Parkinson's disease control group<br>Healthy controls | sBP, HR, RR intervals (Valsalva maneuver and orthostatic stress), muscle strength using one repetition maximum. | Compared with baseline, sBP fall was significantly reduced in the Parkinson's disease training group (14 ± 11 mmHg versus -6 ± 10 |

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| | | Age range: 63 (±8) (Parkinson's Disease Control Group)<br>Age range: 68 (±10) (healthy controls) | | | | mmHg; Parkinson's disease control: -12 ± 10 mmHg versus 11 ± 10 mmHg; interaction *P*<0.05)<br>In addition, after 12 weeks, these parameters in the Parkinson's disease training group achieved values similar to those in the health control group.) |

| Study | Country and setting | Participant characteristics | Group A description and sample | Group B description and sample | Exposures/variables measured | Description of main results |
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| Galizia et al., 2013[62] Case control study | Italy, rehabilitation hospital | N=42 elderly (subset of n=90 diagnosed with orthostatic hypotension and proceeded to "active phase") (4 male)<br>Mean age: 76.8 (±7.9) years | N=21 performed 10 full extensions of the ankle, knee, and hip joints of both limbs against a resistance band (6 kg load) held under their feet while supine in bed | N=21 underwent testing, but did not perform any exercise prior to testing BP and HR | sBP and dBP after 10 minutes supine rest, immediately upon standing up, and after one, three and five minutes standing, HR, self-report orthostatic symptoms. Pre- and post-intervention. Medications taken at time of testing and intervention were recorded. | The reduction of sBP was significantly smaller (*P*<0.01) at each time interval after standing up in the exercise group than in the control group (10 mmHg in the exercises group versus 27 mmHg in the control group), but no difference observed in dBP or HR. Trend towards fewer OH symptoms in the exercise group compared to control during active testing (not significant). |

| Study | Country and setting | Participant characteristics | Groups | Outcomes measured | Main description of results |
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| Lopes et al., 1984[78] | USA, inpatient in Veterans | N=12 spinal cord injury (12 male) | N=6 experimental group performed upper limb exercises while undergoing | BP and HR at 30 secs, 1.5, 2.5, three, four and five-minute intervals during tilt training. | Pre-test termination angle score homogenous between experimental |

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| Quasi-experimental | Administration Medical Center | Experimental group: n=5 with quadriplegia; n=1 with paraplegia; mean time since injury 7.2 weeks Mean age: 40.3 years<br>Control group: n=6 with quadriplegia; mean time since injury 8.2 weeks Mean age: 22.5 years | orthostatic training (tilted from 0 to 70 degrees at 10-degree increments at five-minute intervals on a tilt table)<br>N=6 control group underwent orthostatic training (tilted from 0 to 70 degrees at 10 degree increments at five-minute intervals on a tilt table) | Each participant received a score 1-10 depending on step level at which they experienced OH (at which time the test was terminated). Credit was given for partial completion of time specified at each angle by awarding 0.2 of a score for each 30-second period completed. | and control groups ($P$<0.1). Mean differences in the termination angle. Active, reciprocal, bilateral extremity exercise does not result in a significant change in tolerance of progressively higher vertical angles of tilt. The experimental group did not show increases in BP or demonstrate improved orthostatic tilt tolerance over the control group. Control group mean BP was 122/70 mmHg and experimental group was 117/76 mmHg. |

## Electrical stimulation

| Study | Country and setting | Participant characteristics | Groups | Outcomes measured | Main description of results |
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| Faghri and Yount, 2002[71] Randomized controlled trial Repeated measures | USA, laboratory | N=14 SCI (n=7 paraplegic, n=7 tetraplegic; n=4 incomplete, n=10 complete) (11 male) n=15 healthy able-bodied (gender not reported) Mean age at SCI: 35 (±9.41) years Mean age able-bodied: 29 (±6) years | Fourteen SCI participants used a standing system: stationary standing for 30 minutes and dynamic standing using FES for 30 minutes. Four electrodes, balanced symmetrical biphasic waveform with 35 Hz frequency, duty cycles of 11 seconds on, 60 seconds off for channel 1 (tibialis anterior and gastrocnemius muscles) and 7 seconds on and 64 seconds off for channel 2 (quadriceps and hamstrings muscle groups). Fifteen able-bodied participants performed stationary standing for 30 minutes and voluntary tiptoe contractions during 30 minutes of standing. | Stroke volume, cardiac output, HR, sBP, dBP, TPR, MAP: measured in sitting, standing, after five minutes and 30 minutes of standing in all participants for both static and dynamic standing. | Significant reduction in sBP and dBP ($P$<0.05) and MAP during stationary standing in SCI subjects, while maintained in able-bodied. All BP values were maintained to pre-standing levels in SCI group during standing with FES. No changes in any variables for able-bodied participants. SCI participants demonstrated significant reductions ($P$<0.05) in all hemodynamic values for stationary standing at five and 30 minutes (able bodied-reduction in SV and cardiac output at 30 minutes); compared to no change at five minutes when standing with FES, but at 30 minutes standing with FES there was significant increase in hemodynamic values (HR and SV); able-bodied group maintained at five minutes, but at 30 minutes dynamic standing cardiac output decreased and HR increased. |

| Study | Country and Setting | Participant characteristics | Groups | Outcomes measured | Main description of results |
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| Faghri et al., 2001[77] Quasi-experimental | USA, rehabilitation hospital | N=14: SCI (n=7 paraplegic, n=7 tetraplegic; n=4 incomplete, n=10 | SCI participants used a standing system for stationary standing for 30 minutes and dynamic standing using FES for 30 minutes (active standing | Central hemodynamic responses of SV, cardiac output, HR, MAP, TPR, and rate pressure product during supine, sitting, and standing | Overall, the tetraplegic group had a significantly lower sBP ($P$=0.013) and MAP ($P$=0.048) than the paraplegic group during passive standing. These differences were not detected during active standing. |

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| Repeated measures | | complete) (11 male)<br>n=15 healthy able-bodied (gender not reported)<br>Mean age SCI: 35 (±9.41) years<br>Mean age able-bodied: 29 (±6) years | group). Four electrodes, balanced symmetrical biphasic waveform with 35 Hz frequency, duty cycles of 11 seconds on, 60 seconds off for channel 1 (tibialis anterior and gastrocnemius muscles) and 7 seconds on and 64 seconds off for channel 2 (quadriceps and hamstrings muscle groups).<br>Able-bodied participants performed stationary standing for 30 minutes and voluntary tiptoe contractions during 30 minutes of standing (passive standing group).<br>With versus without order was counterbalanced. | positions, and every five minutes during the 30 minutes standing. | Moving from sitting to standing sBP increased 1.6% in the active standing group compared to a decrease in sBP of 8% in the passive standing group. When data were pooled from both groups and the overall groups response to active and passive standing were compared, the results showed that cardiac output, SV, and BP significantly decreased ($P$<0.05) during 30 minutes of passive standing, whereas TPR significantly increased ($P$<0.05). All hemodynamic variables were maintained during 30 minutes of active standing, and there were increases in rate pressure product and HR after 30 minutes of active standing. |
| Elokda et al., 2000[76]<br>Quasi-experimental | USA, rehabilitation hospital | N=5 SCI, 2 to 4 weeks post-injury (n=2 tetraplegic and n=3 paraplegic) (all male)<br>Age range: 26-36 years | All participants underwent repeated measures: supine on tilt table with feet in contact with footboard. Six minutes rest at 0 degrees for baseline measurements, followed by six 4-minute stages for each tilt angle (0, 15, 30, 45, and 60 degrees), followed by a four minute recovery. Repeated with and without electrical stim (biphasic waveform, 20 Hz frequency without any ramping, alternating 2 seconds on and 4 seconds off periods of the quadriceps and ankle plantar flexors during the tilting procedure)<br>Test terminated if sBP < 60 or dBP < 40 or severe orthostatic | sBP, dBP, and HR taken at one-minute intervals during resting and tilting procedures (tilt angles: 0, 15, 30, 45, and 60 degrees).<br>Subjective perception of orthostatic tolerance measured at one-minute intervals during tilting. | sBP showed a progressive decrease with increasing tilt angle without the electrical stimulation. The electrical stimulation treatment appeared to attenuate the rate of sBP decrease. sBP at each degree of tilt with functional neuromuscular stimulation was higher. dBP was lower for all tilt angles without functional neuromuscular stimulation. |

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| | | | symptoms reported (fainting/headache). | | |
| Hamzaid et al. 2015[89] Quasi-experimental | Malaysia, rehabilitation ward in medical center and at one subject's residence after discharge | N=2 sub-acute SCI (C7), 2 weeks since injury (both male)<br>Age: 62 and 65 years | Both participants underwent four weeks of ES therapy, four times per week for one hour per day. ES was applied on the rectus abdominis, quadriceps, hamstrings, and gastrocnemius with 35 Hz frequency, pulse width 250 μs. The current amplitude was increased incrementally from 0 mA to the maximum tolerated by patients, which was 130 mA. | sBP and dBP pre- and post-testing, every minute 0 to 65 degrees on tilt table, MAP and HR were obtained during pre-test and post-tests with and without ES-evoked muscle contractions. Symptom Scale Questionnaire for Orthostatic Intolerance was conducted during all tests to measure their OH symptoms. | Subject A improved his orthostatic symptoms, but did not recover from clinically defined OH based on the 20-minute duration requirement. With concurrent ES therapy, 60 degrees head-up tilt BP was 89/62 mmHg compared with baseline BP of 115/71 mmHg. Subject B fully recovered from OH demonstrated by BP of 105/71 mmHg during the 60-degrees head-up tilt compared with baseline BP of 124/77 mmHg. Both patients demonstrated longer tolerance time during head-up tilt with concomitant ES (subject A: pre-test = four minutes, post-test without ES = six minutes, post-test with ES = 12 minutes; subject B: pre-test = four minutes, post-test without ES = 28 minutes, post-test with ES = 60 minutes). |
| Kuznetsov et al., 2013[90] Quasi experimental | Russia, inpatient stroke rehabilitation unit | N=128 mild or moderate stroke 4.6 ± 1.2 days post-stroke (56 male)<br>Mean age: 58.3 (±1.2) years | N=38 were treated with ROBO-FES (robotic tilt table and functional electrical stimulation) for 30 days. A six channel stimulator was used and electrodes placed over biceps femoris, quadriceps femoris and gastrocnemius of either leg. Stimulation was synchronized with robotic leg movements varying between 5 and 100 mA.<br>N=35 were treated with ROBO (robotic tilt table only)<br>N=31 were the control group<br>N=24 dropped out | British Medical Research Council Strength Scale, sBP and dBP, SV, cerebral blood flow using transcranial Doppler ultrasonography, Barthel Index for activities of daily living, pulsatility index, resistance index.<br>All measures taken at baseline and post-intervention | None of the participants in the ROBO or ROBO-FES groups had OH or orthostatic reactions when put into a vertical position, but 52% of the control participants showed OH. Did not state whether participants were doing any standing/vertical activities in the usual therapy as part of their rehabilitation. |
| Yoshida et al., 2013[85] Quasi-experimental | Canada, outpatient rehabilitation center | N=10 SCI; n=4 cervical, n=6 thoracic ; 1-29 | N=10 underwent the same testing and acted as their own control. Tilted head-up to 70 degrees from supine; four 10- | Participant report of any symptoms of orthostatic hypotension, such as headache, dizziness, and | sBP decreased significantly during head-up tilt and increased significantly during dynamic FES, especially toward the end. dBP increased significantly during passive |

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| | | years since injury (6 male)<br>Age range: 27-59 years | minute conditions involved, with a 10-minute rest between each condition: 1) passive head-up tilt with no intervention, 2) passive stepping using a motorized stepper (described in intervention section) 3) isometric FES of leg muscles (described in intervention section), and 4) dynamic FES of leg muscles combined with passive stepping (described in intervention section).<br>FES was applied to four muscle groups: tibialis anterior, hamstring, quadriceps femoris and triceps surae of both legs. Stimulation was bipolar and biphasic, with a maximum pulse width of 300 μs and stimulation frequency of 40 Hz. | light-headedness. Inferior vena cava imaging in the transverse plane. Electromyography signals of the leg muscles were recorded only during passive stepping because cyclic passive movements of the legs can induce rhythmical electromyography activities. Beat-to-beat BP recorded non-invasively every minute for 10 minutes during each of the testing conditions. | stepping and dynamic FES. Mean BP increased significantly only during dynamic FES. Statistical significance data for individual conditions not provided. However, results of a three-way ANOVA demonstrate that sBP, mean BP, and HR all increased significantly ($P$=0.004, $P$=0.006 and $P$=0.026) during FES. Passive stepping significantly increased sBP, dBP, and mean BP ($P$=0.009, $P$=0.182, $P$=0.0102).<br>The effects of FES on SV and mean BP were greater than those of passive stepping. When combined, FES and passive stepping did not interfere with each other, but did not synergistically increase SV or mean BP.<br>Thus, the present study suggests that FES delivered to lower limbs can be used in individuals with SCI to help them withstand orthostatic stress. |
| Phillips et al. 2018[84]<br>Quasi-experimental | Canada, laboratory | N=5 SCI; n=4 cervical, n=1 thoracic), 3 years post-injury, (3 male), all with OH<br>Age range: 23-32 years | All participants underwent the same testing, attending two testing sessions separated by at least one day.<br>Once OH occurred, transcutaneous stimulation was applied to the skin between thoracic 7-8 spinous processes. The stimulation was delivered at 30Hz as monophasic, 1-ms pulses, to provide afferent input to the region of the spinal cord where sympathetic preganglionic neuron cell bodies are located. The current was increased from 10 mA until BP normalized, up to a maximum | Following 10 minutes of rest in supine, the test began with 15 minutes of supine measurements, after which participants were passively moved to the sit-up position and supported while sBP, dBP, and HR measurements were recorded for an additional 15 minutes.<br>Participants ranked their symptoms of nausea/ dizziness one to 10 (10 being most severe) each minute of the test | During the orthostatic challenge, all individuals experienced hypotension characterized by a 37 ± 4 mm Hg decrease in sBP, a 52 ± 10% reduction in cardiac contractility, and a 23 ± 6% reduction in cerebral blood flow (all $P$<0.05), along with severe self-reported symptoms. Electrical stimulation completely normalized BP, cardiac contractility, cerebral blood flow, and abrogated all symptoms. Non-invasive transcutaneous electrical spinal cord stimulation may be a viable therapy for restoring autonomic cardiovascular control after SCI. |

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| | | | 70 mA, and maintained for at least one minute. Electromyography of the lower-limb skeletal muscles was recorded to confirm skeletal muscle contractions were not occurring and therefore the pressor responses were not attributed to the skeletal muscle pump of the venous vasculature. | | |

## Compression

| Study | Country and setting | Participant characteristics | Experimental intervention | Control intervention | Outcomes measured | Description of main results |
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| Podoleanu et al, 2006[63] Single-blinded randomized controlled trial Participants were blinded to treatment; computer (blocked per center) randomized sequential order of treatments | Italy, hospital clinic | N=21 elderly persons with symptomatic progressive OH (9 male) Mean age: 70 (± 11) years | All 21 underwent same testing conditions. Elastic compression bandage applied over the legs (40-60 mmHg at the ankles and 30-40 mmHg at the hips) for 10 minutes, then an abdominal bandage was added for a further 10 minutes (20-30 mmHg). The modified Italian tilt protocol was used, consisting of 60 degrees passive tilting for 20 minutes followed by 0.4 mg nitroglycerine challenge for a further 20 minutes | During active sham treatment, the same elastic bandages were applied (5 mmHg overall). | SSS-OI (baseline and one-month post-treatment with elastic leg compression stockings. sBP and HR: supine and 60 degrees, pre- and post-leg bandage phase, end of leg plus abdomen phase | In the intervention group, 90% of all participants remained asymptomatic versus 53% in the control group ($P$<0.02). During the month before evaluation, the mean SSS-OI score was 35.2 (± 12.1) with dizziness, weakness and palpitations accounting for 64% of the total score. The SSS-OI score decreased to 22.5 (±11.3) after one month of therapy ($P$<0.01). In the control group, sBP decreased from 125 (±18) mmHg immediately after tilting to 112 (±25) mmHg after 10 minutes of sham leg bandaged and to 106 (± 25) mmHg after 20 minutes despite the addition of sham abdominal bandage. In comparison, active therapy group |

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| | | | when the passive phase failed to induce syncope. Participants were trained and wore compression stockings (40-60 mHg at ankles and 30-40 mmHg at hips) for one month after testing. | | | BP was 129 (±19) mmHg, 127 ±17 mmHg (*P*<0.003vs control), and 127 (±21) mmHg (*P*<0.002 vs. control). |
| Vijayakumar et al., 2012[88] Randomized controlled trial | India, department of rehabilitation medicine | N=26 acute/sub-acute stroke (duration < 4 weeks post-stroke) with OH (18 male) Mean age: 59.77 (±17.03) years in intervention group and 63.33 (±15.83) in control group | N=13 received pneumatic abdominal binder 40 mmHg pressure and pneumatic calf compression 30 mmHg pressure | N=13 received elastic compression bandaging from the metatarsal head to the popliteal fossa in a single layer spiral manner with overlap | Number of days taken to attain orthostatic stability modified Rankin scale to measure independence of specific tasks. Hemodynamic responses, measuring sBP and dBP, and HR parameters at 0, 30, 45, and 60 degrees tilt. | The percentage of participants <4 weeks post-stroke wearing pneumatic abdominal binder and pneumatic calf compression achieving orthostatic stability was significant on the third (50%; *P*<0.019) and sixth day (100%; *P*<0.007). No significant difference in the modified Rankin scale scores between groups. |
| Fanciulli et al., 2016[67] Single-blind crossover RCT | Austria, community | N=15 with Parkinson's disease and orthostatic hypotension; (8 male) Age range: 66-75 years | After 3 days of testing, all participants received an elastic abdominal binder (20 ± 2 mm Hg pressure). Binder worn for two hours and then assessed (pre- and post). After a one-day interval abdominal binder (20 ± 2 mmHg) worn daily (daytime) for four weeks. | All participants underwent baseline tilt-testing, wore an abdominal binder (20 ±2 mm Hg pressure) or placebo binder (3 ±2 mm Hg pressure applied on the abdominal wall) for two hours, re-tested on the tilt table and subsequently removed the binder. After one-day washout, the tests were repeated to ensure all participants | *Primary:* mean BP changes at 3, 5, and 10 minutes in supine, 60 degrees verticalization and active standing. *Secondary:* Orthostatic Hypotension Questionnaire, Orthostatic Hypotension Symptom Assessment and Orthostatic Hypotension Daily Activity Scale scores after 4-week open-label period. | Compared to the placebo binder, the abdominal binder was associated with an increase of the third minute tilt mean BP by 10 ± 10.2 mmHg; +3.5, +14.5 (*P*<0.006). During the open-label phase, 12 patients wore the abdominal binder an average of 5.6 ± 0.6 days/week, 50% to 75% of daytime. At 4-week follow-up, the Orthostatic Hypotension Questionnaire score decreased by -2.2 points (*P*<0.003), the Orthostatic Hypotension Symptom Assessment (OHSA) |

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| | | | | had been tested in both abdominal and placebo binder. Participants then wore an abdominal binder (20 ± 2 mmHg pressure applied on the abdominal wall) every day during the daytime for four weeks | | sub score by -1.7 points (*P*< 0.003) and the Orthostatic Hypotension Daily Activity Scale by -3.9 (*P*< 0.007). No side effects occurred during the crossover phase. |
| Wadsworth, 2012[92] Randomized crossover trial | Australia, large university-affiliated referral hospital | N=14, SCI T5 or above<br>Age range: 18-73 years | Abdominal binder fitted to provided firm support around the abdomen from the anterior superior iliac crest to the costal margin of the rib cage (no mmHg pressure provided). Participants wore the abdominal binder daily for the duration of the trial (6 months)<br>N=3 participants ceased wearing the binder daily. No data provided on daily wearing time. | Participants acted as their own controls and underwent testing in both conditions | MAP<br>Respiratory measures (peak expiratory flow, forced expiratory flow, forced vital capacity)<br>Voice measures<br>Measured at three time points: six weeks, three and six months, in supine and sitting in own wheelchair. | There was no statistically significant improvement in MAP, maximal expiratory pressure or sound pressure level.<br>Overall, an abdominal binder resulted in a statistically significant improvement in forced vital capacity (*P*<0.005), forced expiratory volume in one second (*P*<0.05), peak expiratory flow (*P*<0.02), maximal inspiratory pressure (*P*<0.01), and maximum sustained vowel time (*P*<0.01). |
| Gorelik et al., 2004[81] Randomized crossover trial | Israel, hospital inpatient | N=61 admitted with acute medical conditions requiring bed rest (n=11 acute coronary syndrome; n=10 pulmonary edema; n=14 cerebrovascular accident; n=21 | All participants underwent testing with or without compression bandages applied to both legs from ankle to thigh before moving from supine to seating. Extensible bandages were used obtain a uniform pressure of | | BP, ECG tracing, HR, $O_2$ saturation, dizziness, and palpitations were recorded prior to seating and during one, three, and five minutes in sitting. | Prevalence of postural hypotension was identical in the unbandaged versus bandaged state (55.7%). However, dizziness, palpitations, accelerated HR, and decreased $O_2$ saturation over five minutes were more prevalent in the unbandaged versus bandaged state (*P*<0.01, *P*<0.001, *P*<0.05, |

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| | | infectious diseases; other n=5) (41 male) Mean age: 77.8 (±9.7) years | about 30 mmHg. The bandages were stretched along both legs so that the designed rectangles were transformed into squares. | | | *P*<0.001, respectively). In the unbandaged state, presence versus absence of OH was associated with significantly greater incidence of palpitations, tachycardia and decline of $O_2$ saturation over time (*P*< 0.04, *P*<0.03, *P*<0.03, respectively). |

| **Study** | **Country and setting** | **Participant characteristics** | **Groups** | **Outcomes measured** | **Main description of results** |
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| Gorelik et al., 2009[82] Quasi-experimental | Israel, inpatient medical department | N=108 acute decompensated heart failure (n=53 postural hypotension, n=27 dizziness and/or palpitations, n=10 cardiac arrhythmias) (48 male) Mean age: 75.1 (± 8.3) years | Compression extensible bandages were applied along both legs from the ankle to the thigh before seating. The bandages were stretched so that the designed rectangles were transformed into squares to obtain a uniform pressure (40 mm Hg at the ankle). All participants underwent the same testing: two sessions. Day 1 bandages but without compression. Day 2 compression bandages of approximately 40 mmHg pressure. Participants assisted from supine to sitting, not standing | BP, HR, $O_2$ saturation, and the occurrence of dizziness or palpitations were recorded prior to, and during one, three, and five minutes in sitting. | Compression bandages prevented postural hypotension in 21 of 49 patients and decreased the degree of postural BP fall (*P*<0.001). sBP and dBP were higher in the bandaged group following one minute of sitting (sBP: 146.6 ± 31.1 mmHg bandaged versus 141 ± 28.1 mmHg unbandaged; *P*=0.055; dBP: 72 ± 13.9 mmHg bandaged versus 68.7 ± 16.9 mmHg unbandaged; *P*=0.05) and following five minutes of sitting (sBP: 147 ± 28.6 mmHg bandaged versus 141 ± 27.1; *P*=0.03; dBP: 72.4±14.6 bandaged versus 67.9 ± 17.4 mmHg unbandaged; *P*=0.01). |
| Gorelik et al., 2014[83] Quasi-experimental | Israel, hospital inpatient | N=73 bedridden for ≥8 hours with diagnosed OH with various acute medical conditions (22 male) | Before moving from supine into sitting, compression extensible bandages were stretched along both legs from the ankle to the end of the thigh, so that the designed rectangles became transformed into squares, to | sBP and dBP, heart rhythm with ECG, self-report symptoms of OH in supine and at one, three and five minutes of sitting. | Compared with the non-bandaged state, OH was registered in only 53.4% of bandaged participants (*P*<0.001). Moreover, the appearance of OH symptoms decreased to 34.2% (*P*<0.001).<br>On the second day (bandaged), supine dBP values were higher in the persisting 82.1 ± |

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| | | Mean age: 75.2 (±9.0) years | obtain a uniform pressure of about 30-40 mmHg at the ankle. All participants underwent same testing: day 1 no compression, day 2 compression. | | 18 mmHg versus non-persisting OH group 73.6 ± 14 mmHg (*P*<0.027). In the bandaged state, OH symptoms were significantly reduced in the non-persisting OH group 35.3% (*P*<0.003).<br>In participants with persistent OH, sBP was significantly increased wearing bandages (147.0 ± 28 mmHg) versus unbandaged (136.2 ± 26.5 mmHg) (*P*<0.004). |
| Henry et al., 1999[51]<br>Quasi-experimental | United Kingdom, outpatient falls clinic | N=10 elderly with OH (6 male)<br>Age range: 62-89 years (mean 77.2 years) | All participants underwent same testing: supine rest then positioned into standing 90 degrees upright with tilt table for 3 minutes, then positioned into supine. Elastic compression hosiery (tights) fitted to bilateral lower limbs. | sBP and dBP, HR in supine; one, two and three minutes in supine and 90 degrees tilt. Authors refer to the fact that "orthostatic dizziness was abolished in seven out of 10 participants" but do not report how this was measured. | Short-term efficacy with compression hosiery in elderly people with symptomatic OH and a history of falls. (Not reported if OH was reason for falling or other factors.) |
| Denq et al., 1997[75]<br><br>Quasi-experimental | USA, clinic | N=14 confirmed diagnosis of OH (n=3 multiple system atrophy; n=9 PAF; n=2 diabetic autonomic neuropathy) (5 male)<br>Age range: 31-78 years | All participants underwent testing from supine to 80 degrees head-up tilt ± compression (40 mmHg) to calves/thighs/abdomen and all compartments combined to evaluate the impact compression of different body parts on orthostatic BP and tolerance. | Visual analogue scale (numerical) rating change in symptoms and duration of stand with compression garments; sBP and dBP in supine and 80 degrees verticalization, HR, end diastolic volume index, cardiac output index, and peripheral resistance index. Visual analogue scale of severity of symptoms after each session. | Head-up tilt with compression resulted in significant improvement (*P*<0.001) of sBP 115.9 ± 7.4 mmHg compared to 89.6 ± 7.0 mmHg without compression. Maximum improvement was with all combinations of compression. Abdominal compression alone was the only single compartment to significantly reduce OH (*P*<0.01).<br>Participants reported that a combination of all compartments was most efficacious in reducing symptoms. |
| Lucas et al., 2012[91]<br><br>Quasi-experimental | New Zealand, Laboratory | N=12 healthy elderly people and younger adults<br>N=6 elderly people (6 male) | All 12 participants stood up rapidly (<5 seconds) and remained free standing for three minutes, then returned to supine for six minutes and repeated the supine-to-stand protocol. | Esophageal temperature, skin temperature, blood flow velocity, arterial BP (beat-to-beat changes in BP), cardiac output from HR and SV, TPR in supine and standing. | All participants completed the normothermic and passive heat conditions of both control and compression leggings. No difference in supine or initial seconds in standing in either groups. In minute 6 of standing, those wearing compression leggings in the |

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| | | Mean age: 70 (±4) years<br><br>N=6 younger adults (6 male)<br>Mean age: 29 (±4) years | Standing was terminated and participants positioned supine with legs elevated if presyncope symptoms presented. This was completed at normal body temperature and repeated at elevated body temperature (0.5 degrees Celsius). In the elevated temperature trials participants wore long-sleeved and legged, two-pieced, tube-lined perfusion suit. Passive heating was achieved by circulating warm water through the suit and wrapping participants in reflective foil blanket with periodic warm water circulation to maintain the elevated temperature. | | normothermia increased TPR in older participants but dropped in younger participants. In contrast, standing and heated, wearing compression leggings lowered TPR in elderly people and younger adults. |

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| Rimaud et al., 2012[68]<br>Quasi-experimental | France, department of **physical** medicine and rehabilitation | N=9 SCI (n=4 above T6, n=5 below T6), at least two years post injury (9 male)<br>Age range: 25-54 years | All participants performed two maximal wheelchair exercise tests using a wheelchair ergometer (increasing Watts every 2 minutes) without and with garment compression stockings (21 mmHg (ankle) to 15 mmHg (calf).<br>The progressive wheelchair test started with a 30-minute rest period using the wheelchair ergometer to stabilize various cardiorespiratory variables. This was followed by a six-minute warm up at a constant speed with no load. The load was then increased by 10W increments for low-level paraplegics and 5W for high-level paraplegics, every | $VO_2/VCO_2$ measurement during test, sBP, dBP, finger arterial pressure, SV, Q, TPR, HR variability, wavelet high and low and very low frequency power. All tested pre- and post-exercise sitting in wheelchair, without garment compression stockings and with garment compression stockings. Norepinephrine and epinephrine | No differences in $VO_2$, W max, HR, or BP with or without GCS. Significantly higher ($P$<0.05) low-frequency wavelet and lower high-frequency wavelet (high-frequency wavelet is a parasympathetic marker) with garment compression stockings 3 to 8 minutes post exercise. Decrease in mean relative risk with garment compression stockings immediately after exercise. Norepinephrine at rest was significantly higher ($P$<0.05) with garment compression stockings. Epinephrine and norepinephrine both increased with exercise with and without garment compression stockings. |

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| | | | two minutes until volitional exhaustion, or the subjects were unable to maintain the required speed. | | |
| Helmi et al., 2013[61]<br>Case report | Netherlands, intensive care unit | N=1 post-operative cervical C3/C4 laminectomy tetraplegic with clinically significant compromise of cardiovascular control, (male)<br>Age: 61 years | Tilt-table testing from supine 0 to 45 degrees and 60 degrees and back to supine without, and then with inflatable external leg compression to bilateral lower limbs (calf and thigh). | sBP and dBP in 0, 45, and 60 degrees tilt, SV index, HR, perfusion index, peripheral perfusion tissue oxygenation. | With the application of 15 mmHg pressure during 45 and 60 degrees head up, SV index and HR were maintained, and no presyncope symptoms occurred.<br>With the external leg compression constantly inflated with a pressure of 15 mmHg, the participant could remain in the upright position and could be mobilized during physiotherapy wearing inflatable external leg compression.<br>External leg compression succeeded in improving presyncope symptoms and preventing OH for several hours. |

## Physical counter-maneuvers

| Study | Country and setting | Participant characteristics | Groups | Outcomes measured | Main description of results |
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| Ten Harkel et al., 1994[58]<br><br>Randomized crossover trial | Netherlands, academic medical center | N=13 (n=7 orthostatic hypotension (n=4 PAF, n=1 Hodgkin's disease, n=1 medulla oblongata bleed, n=1 multiple sympathectomies); n=6 healthy controls (11 male)<br>Age range: 20-65 years | Intervention group: leg muscle pumping (tiptoeing) or tensing (leg crossing) for one minute, started after 2 minutes of active standing. Maneuvers were performed in a random order, each for one minute, with one minute of quiet standing in between.<br><br>Control group: active standing | sBP and dBP, HR, SV, cardiac output, peripheral resistance assessed before standing (10 seconds) and after one minute of tiptoe, quiet standing and leg crossing assessed over 10 seconds at first and after one and two minutes in standing. | Mean BP, sBP, and dBP significantly decreased in patient group ($P$<0.01) following one minute of standing; systemic vascular resistance did not change from supine; rise in HR seen mainly in patients due to non-PAF patients.<br>Tiptoeing did not result in a clear distinction between initial and sustained effects between PAF and non-PAF patients.<br>Leg-crossing induced an initial increase in BP, SV, and cardiac output both in normal participants and patients with PAF and non-PAF. There was a small increase in MAP of only 13 mmHg in the patient group, but the |

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| | | | | | authors suggested that this increase is of a similar magnitude to the changes seen in pharmacological interventions such as fludrocortisone, erythropoietin, and midodrine. |
| Bouvette et al., 1996[73] Quasi-experimental | USA, laboratory and community | N=9 with neurogenic OH (n=5 PAF; n=3 autonomic neuropathy; n=1 multiple system atrophy) (4 male) Mean age: 53 (± 18) years | N=9 underwent four training sessions in the laboratory, then performed the physical counter-maneuvers at home for 3-4 months<br>Physical counter-maneuvers: squatting, genuflection-contraction, leg crossing, knee flexion, toe raise, neck flexion, abdominal contraction, thigh contraction.<br>Session 1: all physical counter-maneuvers performed in random order. Sessions 2 and 3 three: biofeedback training on three maneuvers selected by the participant that provided the best symptomatic relief to optimize performance. Session 4: practicing maneuvers without feedback. | Global Symptomatic Improvement Score: judging the effectiveness of physical counter-maneuvers; improvement in orthostatic BP and continued improvement with follow-up telephone survey. BP measured at baseline, before and after each counter-maneuver. | Global Symptomatic Improvement Score: The findings support the hypothesis that physical counter-maneuvers can significantly increase BP. Squatting produced the most dramatic change in arterial pressure (40.6 ±23.2 mmHg) ($P$<0.0004). Continued improvement: Standing time improved by 8.33 ± 5.8 mmHg minutes. Participants reported continued counter-maneuver performance of 3.83 ± 3 .1 mmHg maneuvers per day. Biofeedback training: statistically significant improvement seen with genuflection-contraction ($P$<0.002), leg crossing ($P$<0.016), and thigh contraction ($P$<0.007) after three or four 45-minute sessions. |
| van Lieshout et al., 1992[60] Quasi-experimental | Netherlands, outpatient | N=13 (n=7 hypoadrenergic OH; n=6 healthy)<br>OH (4 male); age range 18-65 years<br>N=6 healthy controls (gender not reported); age range: 28-34 years | All participants performed exercises in fixed order: stand up, cross legs, squat. Stand for 10 minutes maximum or until symptoms occur. Then cross legs for 30 seconds, then resume standing. Squat when "BP became low again" (BP cut off not described). | sBP and dBP measured in all three positions. | Standing without any physical maneuvers, five out of seven participants reported orthostatic dizziness within 10 minutes (four unable to remain standing). After leg-crossing, all participants could stand for 10 minutes or more with a difference of 14 mmHg (SD ± 6) in mean BP. A larger increase in sBP was observed with squatting with a difference of 44 mmHg (SD ± 18). |
| Smit et al., 1997[56] | Netherlands, laboratory | N=8 OH (n=5 autonomic failure, | Each participant sat on seats of varying heights (48 cm, 38 cm, 20 | sBP and dBP, HR, cardiac output, SV, and TPR. | BP was higher in sitting than standing. Due to increase in SV and cardiac output. Lower |

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| Quasi-experimental | | n=2 post-acute panautonomic neuropathy, n=1 post-extensive sympathectomy) (3 male)<br>Age range: 35-70 years | cm) and performed different maneuvers such as squatting, crossing legs, and standing in a crossed-leg position. | All measures taken:<br>Standing: with and without contraction of crossed legs<br>Sitting: with and without leg-crossing sat on Derby chair, Fishing chair, and footstool<br>Squatting | chairs associated with high increment in BP. Crossing legs on the Derby chair produced greater increment in sBP and dBP (*P*<0.01; mean change 16 mmHg and 9 mmHg no leg crossing and 49 mmHg and 25 mmHg with leg crossing). Standing crossing legs increased sBP and dBP significantly (*P*<0.01; 14 mmHg and 7 mmHg standing and no leg crossing versus 29 mmHg and 15 mmHg crossing legs in standing) and in seven out of eight of the participants, produced a higher increase than sitting on the Derby chair. Sitting on a fishing chair was perceived as most comfortable. Derby chair was deemed unstable/did not relieve symptoms/small seat. Low stool was hard to stand up from; uncomfortable or experienced dizziness on standing. |
| Tutaj et al., 2006[93]<br>Quasi-experimental | Country not reported (author was contacted), | N=17 familial dysautonomia (9 male)<br>Mean age: 26.4 (±12.4) years | Physical counter-maneuvers: bending forward, squatting, leg crossing, and abdominal compression using an inflatable belt. Counter-maneuvers were initiated after standing up, when sBP had fallen by 40 mmHg or dBP had fallen by 30mmHg, or presyncope had occurred. | HR, sBP, and dBP, mean BP, cardiac output, TPR, and calf volume | Mean BP increased significantly (*P*<0.005) during bending forward 20.0 mmHg, squatting (*P*<0.002) 50.8 mmHg and abdominal compression 5.8 mmHg (*P*<0.04) but not during leg-crossing. Squatting and abdominal compression also induced a significant increase in cardiac output during squatting (*P*<0.02) 18.1 mmHg and during abdominal compression 7.6 mmHg (*P*<0.014). |

## Physical counter-maneuvers and compression

| Study | Country and setting | Participant characteristics | Groups | Outcomes measured | Main description of results |
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| Smit et al., 2004[57] | Netherlands, laboratory | N=23 neurogenic orthostatic | All participants performed Protocol 1: evaluated in a 40 to | sBP and dBP in supine, 40 degrees head-up-tilt, 15 | Protocol 1 (n=7) head-up tilt from supine. Compression resulted in an increase in BP |

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| Quasi-experimental | | hypotension (n=4 PAF, n=7 multiple system atrophy, n=8 progressive autonomic neuropathy, n=3 subacute panautonomic neuropathy, n=1 OH post extensive sympathectomies) (10 male)<br>Age range: 35-79 years | 60 degree head-up tilt position, the effect of abdominal compression on caval vein and femoral diameter, arterial BP, and hemodynamics wearing an anti-gravity suit.<br>Protocol 2: anti-gravity suit standing, then standing and legs crossed with 20 mmHg abdominal compression, 40 mmHg abdominal compression<br>All participants performed protocol 3: investigated the ability to maintain standing BP by an elastic binder (9 or 12 inch), compression 15-20 mmHg | seconds preceding compression, first 15 seconds of 40 mmHg lower abdominal compression, last 15 seconds of 40 mmHg compression, and 5 seconds after compression and in standing with graded pressure 20/40 mmHg ± leg crossing. HR, cardiac output, TPR, and changes in the inferior caval and femoral vein diameter. | with increase in SV and cardiac output and no change in peripheral resistance diameter of veins, decreases caval vein but femoral vein increases.<br>Protocol 2 (n=12) binding and countermeasures increased BP, but there was no significant difference between conditions.<br>Protocol 3 n=9 significant increase in BP ($P$<0.05; 11 mmHg sBP and 6 mmHg dBP) and increase SV (13% $P$<0.05) and cardiac output (12% $P$<0.05) and reduction in peripheral resistance (-7% $P$<0.05)<br>Elastic abdominal compression increased standing BP with 15/6 mmHg (range -3/3 to 36/14, $P$<0.05). |

| Study | Country and setting | Participant characteristics | Experimental intervention | Control intervention | *Outcomes measured* | Description of main results |
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| Figueroa et al., 2015[72] Randomized crossover trial | USA, laboratory | N=13 with neurogenic orthostatic hypotension, (n=5 PAF; n=4 multiple system atrophy; n=2 Parkinson's disease; n=1 post-radiation baroreflex failure; n=1 autoimmune autonomic neuropathy. (7 male)<br>Age range: 62-79 years<br>Participants were ambulatory and able to stand for at least 3 minutes without | Abdominal compression and physical maneuvers<br>All participants performed four maneuvers: moving from supine to standing without abdominal compression; moving from supine to standing with either a conventional or adjustable abdominal binder; application of subject-determined maximum pressure tolerable while | All participants moved from supine to standing without abdominal compression, then with either a conventional or adjustable abdominal binder. The adjustable binder involved the application of participant determined maximum pressure tolerable while standing. Participants were asked to stand up and adjust the | *Primary:* Continuous sBP, dBP, and HR in supine, and standing<br>*Secondary:* Orthostatic Symptom Scale (visual analogue scale); Symptom Change Scale (visual analogue scale) | Standing without abdominal compression resulted in a large orthostatic fall (change in sBP, −57 mmHg) and severe orthostatic intolerance (Orthostatic Symptom Scale, 5 points).<br>Compared with no abdominal binding, 10 mmHg of abdominal compression while supine prior to rising was effective in attenuating OH with both the conventional (change in sBP, −50 mmHg; interquartile range, −33 to −70 mmHg; $P$=<0.03) and pull string (change in sBP, −46 mmHg; |

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| | | developing pre-syncope. | standing; and while still erect, subsequent reduction of compression to a level the subject believed to be tolerable for a prolonged period. | compression to a maximal tolerable level, and then subsequently reduce the compression to a level the subject believed to be tolerable for a prolonged period. It was unclear if this was immediate or within a specific time of standing. | | interquartile range, −34 to −75 mmHg; *P*<0.01) binders. |

## Sleeping with head up

| Study | Country and setting | Participant characteristics | Groups | Outcomes measured | Main description of results |
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| Ten Harkel et al., 1992[59] Quasi-experimental | Netherlands, academic center (two patients were tested on an outpatient basis, while the other four were admitted to hospital) | N=6 hypoadrenergic OH (3 male) Age range: 23-65 years | Each patient received a diet containing 150-200 mmol sodium and a minimal water intake of 2000 mL per day. This three-week study was divided into one-week phases. To assess changes during the steady state alone, the first three days of each week were excluded from the analysis; values were presented as the average for the last four days of each period. Interventions were delivered in one-week blocks. In the first week (control), they did not have medication (apart from two bedridden patients because of severe OH who had 0.1 mg fludrocortisone) or head tilt. In the second week, all patients started to sleep in the 12 degrees head-up tilt position. During the third week treatment involved a combination of sleeping in the head-up tilt position and fludrocortisone administered at 2200 hours. | Orthostatic tolerance as measured by Orthostatic Disability Score; maximum standing time, terminated either at the onset of severe orthostatic dizziness or after a maximum period of 10-minute standing; sBP, dBP, and mean BP) for control; head-up tilt; head-up tilt and fludrocortisone, and follow-up; fluid balance (changes in total body water content assessed by measuring changes in body weight). Follow-up at 14 months. | Combined treatment reduced orthostatic dizziness in all patients ($P < 0.001$), and increased the maximal standing period to at least 10 minutes. Head-up tilt alone (n=4) reduced the BP decrease after 1 minute of standing from -64/-42/-25 ± 27/21/17 mmHg to -53/-37/-23 ± 31/24/20 mmHg ($P<0.01$ for sBP). The addition of fludrocortisone to head-up tilt (head-up tilt/fludrocortisone) (n=5) further reduced the BP decrease after one minute of standing from -63/-40/-24 ± 20/12/11 mmHg to -21/-19/-8 ± 12/10/5 ($P<0.05$ for sBP, mean and dBP). BP at maximal standing time increased during combined treatment 58/47/42 ± 9/8/7 mmHg initially to 95/69/57 ± 27/22/20 mmHg ($P<0.05$ for sBP and mean BP), and remained unchanged during the 14-month (range 8-70 month) follow-up period. |
| Fan et al., 2011[55] Randomized controlled trial | Ireland, community | N=100 with OH Mean age: 76 years | Intervention group n=66, control group n=34 Intervention group had the head of their bed elevated six inches with blocks for six weeks. | Hemodynamic variables: sBP, dBP (24-hour ambulatory blood pressure), MAP, HR, cardiac output, SV, TPR. Plus weight, frequency of dizziness, 24- | Sleeping with head up six inches for six weeks was tolerated by participants and both groups reported overall improvement and had fewer episodes of dizziness per week before versus after ($P=0.0039$). Participants sleeping with head up were more likely to |

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| | | | | hour urinary sodium and volume, and presence of ankle edema. | have leg edema. Compliance to the treatment was 77%.<br>However, there were no significant differences between the two groups in hemodynamic variables. Changes in sBP between pre and post were: -1.45 mmHg supine and 1.98 mmHg standing; dBP 2.42 mmHg supine and 2.61 mmHg standing, MAP 0.94 mmHg sitting and 2.07 mmHg standing.<br>Study concluded that sleeping head up six inches for six weeks is not recommended as an outpatient treatment for OH in elderly people. |

# Dietary measures

## Food intake

| Study | Country and setting | Participant characteristics | Groups | Outcomes measured | Main description of results |
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| Loew F et al., 1995[70] Quasi-experimental | Switzerland, teaching hospital | N=10 Parkinson's disease (n=2 diagnosed with OH) (5 male) Mean age: 81.6 (± 9.02) years<br><br>N=10 age matched hospital in-patient controls (3 male) Mean age: 85.3 (± 5.23) years | Testing over two consecutive days. Day 1: BP monitoring every 30 minutes in supine between 0800 and 1800 hours. Supine sBP readings were used before the start of lunch and 60 minutes after a normal 2500 kj lunch to measure the postprandial sBP change Day 2: participants received their usual breakfast and pursued their usual activities in the ward (newspaper reading or rest). Participants with Parkinson's disease received their usual physio mid-morning and afternoon, orthostatic BP in active standing and head-up tilting tests performed after a normal 2500 kj lunch (lunch eaten in sitting). All participants underwent orthostatic tests: active standing and head-up tilting tests, performed 60 and 40 minutes before the start of lunch. | sBP, HR in supine, active standing and head-up tilt testing both pre- and post-prandial. dBP was recorded but not presented in the literature. Day 1 BP testing in supine, day 2 testing in sitting. | Participants with Parkinson's disease had a significant ($P$<0.01) postprandial sBP drop from 154.3 ± 26.2 to 127.7 ± 18.1 mmHg in supine position compared to healthy controls; in participants with Parkinson's disease, the drop was moderately correlated to orthostatic sBP responses and significantly correlated to the pre-prandial supine baseline systolic BP. There was a greater fall of sBP with passive than with active standing with both groups, which was greater in the PD group. No difference in orthostatic HR responses between groups. |
| Mader SL, 1989[79] Observational | USA, clinical research center | N=26 healthy elderly and young adults (16 male) | All participants underwent the same testing: three recumbent BPs measured two minutes apart after five minutes supine | sBP and dBP, HR | Supine BP: elderly had higher sBP and dBP. HR was higher in both groups after meals. Standing sBP and dBP was similar between groups. The younger group had higher HR |

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| | | N=10 healthy young<br>Age range: 19-31 years<br><br>N=16 healthy elderly<br>Age range: 55-78 years | rest. The subject stood up and BP was measured one minute later. Protocol was performed beginning at 2:30 p.m. on admission and 1:00 p.m. the following day at discharge. Readings included first thing in the morning 7:00 am, before and after meals, mid-morning, mid-afternoon, mid evening and bedtime (10:30 p.m.). Postural BP protocol was performed 45 minutes after the beginning of each meal. | | with standing. Elderly people showed drop pre- to post-meal BP (not seen in young). HR was higher post-meal in both groups. After overnight rest, standing BP was the same. |
| Puvi-Rajasingham S and Mathias CJ, 1996[53]<br>Quasi-experimental | United Kingdom, inpatient | N=7 primary autonomic failure with severe OH (n=3 PAF with no other neurological deficit; n=4 Shy-Drager syndrome (multiple system atrophy) (4 male)<br>Age range: 45-69 years | All participants underwent same conditions: first day 3 meals, versus second day (at least one day apart) 6 meals. Total calorie intake was the same. | BP monitoring and self-initiated readings after five minutes of lying, sitting, or standing. With only three meals, participants have extra set of positional recordings (six in total same as a six-meal day).<br>Participants kept a symptom diary. | Regardless of meal the size, drop in BP with positional change was similar but three meals showed a significantly lower BP in all positions than six meals (131 mmHg after large meals and 151 mmHg after small meals $P<0.005$).<br>Between meals, a larger drop in BP was seen with three meals (sBP: 88 mmHg versus 104 mmHg, $P<0.002$; dBP: 48 mmHg versus 63 mmHg, $P<0.0001$). Fewer OH symptoms were experienced with six meals. |

## Fluid intake

### Fluid intake and exercise

| Study | Country and setting | Participant characteristics | Groups | Outcomes measured | Main description of results |
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| Humm AM et al., 2008[52]<br><br>Quasi-experimental | United Kingdom, laboratory | N=8 PAF diagnosed with OH, all able to walk (3 male)<br>Mean age: 63.9 (±6.1) years | All participants underwent same testing: supine 10 minutes rest, standing 10 minutes, rest in supine, exercises in supine (pedal ergometer), rest in supine, standing five minutes. Identical protocol followed on two separate occasions: one of which participants drank 480 mL distilled water at room temperature within five minutes after first stand. Participants were randomly assigned to start with the protocol without water (n=3) and with water (n=5) with on average 10.8 days between the two assessments. Participants were asked to drink the water within five minutes. | sBP and dBP in supine one (rest), standing one (five minutes standing), supine two (rest), cycling (exercise), supine three (rest), stand two.<br>HR, subjective perception of hypotension related symptoms. | All participants had severe OH pre-exercise with prompt recovery of BP in supine. Five minutes after drinking water, there was a significant ($P$<0.05) rise in BP in supine position. With exercise there was a clear fall in BP (sBP: 42.1 ± 24.4 mmHg and dBP: 25.9 ± 10.0 mmHg) with a modest risk in HR; this occurred even after water ingestion. sBP remained low after exercise but was significantly higher ($P$<0.05) after water intake two and five minutes of standing (74.5 ± 32.9 mmHg) and 74.3 ± 28.4 mmHg without water versus 103.5 ± 34.4 mmHg 89.0 ± 16.7 mmHg with water), resulting in better tolerance of post-exercise standing. |
| Shannon et al., 2002[66]<br><br>Quasi-experimental | Germany, laboratory | N=18 primary autonomic failure (n=9 PAF, n=9 multiple system atrophy) (12 male)<br>Age range: 35-70 years<br>Plus an additional n=9 females with idiopathic orthostatic intolerance<br>Mean age: 36 (± 4) years | Participants drank 120 mL, 240 mL, and 480 mL of tap water at room temperature (20 degrees Celsius) in less than five minutes on separate days.<br>All participants underwent Protocol 1: drinking 480 mL of tap water at room temperature (20 degrees C) in less than 5 minutes.<br>All participants underwent Protocol 2: consumption of standardized high carbohydrate breakfast. | Blood pressure (supine, seated, upright); HR<br><br>Protocol 1: seated, BP, and HR measured every five minutes for 30 minutes, standing, returned to seated for a further 35 minutes with BP and HR taken every five minutes, standing BP determined.<br><br>Protocol 2: seated for 30 minutes and BP and HR taken every five minutes, participants ate a meal, then BP and HR taken every five minutes for 90 minutes while seated. Repeated twice (once with water before the meal, one meal only). | Before water drinking, seated BP was 117 ± 23/67 ± 10 mmHg, which fell to 83 ± 20/53 ± 11 mmHg after one minute of standing. Thirty-five minutes after drinking 480 mL of water at room temperature in less than five minutes, seated BP increased to 150 ± 25/78 ±13 mmHg and after standing for one minute BP was 114 ± 30/66 ± 18 mmHg.<br>Pre-meal BP 138 ± 41/77 ± 17 mmHg. Within 20 minutes after starting to eat, BP decreased, reaching a nadir of 43 ± 36/20 ± 13 mmHg below baseline after 90 minutes. Drinking 480 mL of water in less than five minutes prior to a test meal, BP increased with a peak that was 36 ± 23/9 ± 10 mmHg above baseline after 20 minutes ($P$<0.001 ANOVA compared to meal with no water). Drinking water attenuated orthostatic tachycardia in patients with idiopathic |

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| | | | | Valsalva maneuver, hyperventilation, cold pressor, hand grip. | orthostatic intolerance (123 ± 23 beats per minute at baseline to 108 ± 21 beats per minute after water drinking.)<br>(Inconsistencies in reported number of participants between the methods and participant characteristics.) |
| Young and Mathias, 2004[54]<br><br>Quasi-experimental | United Kingdom, inpatient neurological hospital | N=14 chronic autonomic failure and severe OH<br>(n=7 multiple system atrophy) (4 male)<br>Mean age: 62 (±9.5) years<br><br>(n=7 PAF) (3 male)<br>Mean age: 59 (±10) years | All 14 participants underwent the same testing: standing BP and HR were measured before and 15 and 35 minutes following ingestion of 480 mL distilled water within five minutes. Patients remained seated for 15 minutes after water ingestion, with beat to beat cardiovascular indices measured with the Portapres 2 device with subsequent Modelflow analysis. | sBP and dBP before, and 15 and 35 minutes after ingestion of 480 mL distilled water.<br>Calculation of cardiac output, TPR, and SV using Modelflow analysis. | Standing prior to water ingestion caused a significant fall in sBP in all patients (110.6 ± 25.1 mmHg seated and 79.5 ±21.5 mmHg standing; *P*<0.01). After water ingestion, standing sBP was significantly higher (*P*<0.001) at 15 minutes (101.0 ± 23.3 mmHg) and 35 minutes (99.6 ± 24.0 mmHg), with an improvement in orthostatic symptoms.<br>The time to first significant rise in seated BP occurred at five minutes post-water ingestion in PAF and at 13 minutes in multiple system atrophy. These increases were accompanied by increases in total minutes post peripheral resistance, reaching significance by five minutes in PAF and 13 minutes in multiple system atrophy. There were no significant changes in cardiac output, SV, or ejection fraction. |

BP: blood pressure; dBP: diastolic blood pressure; ECG: electrocardiogram; FES: functional electrical stimulation; HR: heart rate; $O_2$: oxygen; OH: orthostatic hypotension; PAF; pure autonomic failure; RR: intervals between successive heartbeats; sBP: systolic blood pressure; SCI: spinal cord injury; SSS-OI: Specific Symptom Scale Questionnaire for Orthostatic Intolerance; SV: stroke volume; TPR: total peripheral resistance; $VCO_2$: maximum rate of expired carbon dioxide; $VO_2$: maximum rate of oxygen consumption

**Table 1: Critical appraisal results of eligible randomized controlled trials**

| Citation | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Q12 | Q13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fanciulli et al[67] | U | N | Y | U | N | N | Y | Y | U | Y | Y | Y | Y |
| Faghri & Yount[71] | N | N | N | N | N | N | Y | N | Y | Y | Y | Y | N |
| Figueroa et al[72] | U | U | Y | N | N | U | Y | Y | N | Y | Y | Y | Y |
| Fan et al[55] | U | U | Y | N | U | U | Y | N | Y | Y | Y | Y | N |
| Kanegusuku[87] | Y | Y | Y | N | N | N | Y | Y | Y | Y | Y | Y | Y |
| Gorelik et al[81] | U | U | Y | N | N | U | Y | Y | U | Y | Y | Y | Y |
| Luther et al[65] | Y | N | Y | N | N | N | Y | N | Y | Y | Y | Y | Y |
| Phillips et al[84] | Y | Y | U | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Podoleanu et al[63] | Y | Y | Y | Y | N | N | Y | Y | Y | Y | Y | Y | Y |
| Rocca et al[69] | Y | Y | N | N | N | U | Y | Y | Y | Y | Y | Y | Y |
| Takahagi et al[86] | U | U | Y | N | U | U | Y | Y | Y | Y | Y | Y | Y |
| Taveggia et al[64] | Y | N | Y | N | N | N | Y | Y | Y | Y | Y | Y | Y |
| Vijayakumar et al[88] | U | Y | Y | U | U | U | Y | U | U | Y | U | Y | Y |
| Total % | 46.15 | 38.46 | 76.92 | 15.38 | 7.69 | 7.69 | 100.0 | 69.23 | 69.23 | 100.0 | 92.3 | 100.0 | 84.61 |
| | | | | | | | | | | | | | |

Y = Yes, N = No, U = Unclear; JBI critical appraisal checklist for randomized controlled trials: Q1 = Was true randomization used for assignment of participants to treatment groups?; Q2 = Was allocation to treatment groups concealed?; Q3 = Were treatment groups similar at baseline?; Q4 = Were participants blind to treatment assignment?; Q5 = Were those delivering treatment blind to treatment assignment?; Q6 = Were outcome assessors blind to treatment assignment?; Q7 = Were treatment groups treated identically other than the intervention of interest?; Q8 = Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?; Q9 = Were participants analyzed in the groups to which they were randomized?; Q10 = Were outcomes measured in the same way for treatment groups?; Q11 = Were outcomes measured in a reliable way?; Q12 = Was appropriate statistical analysis used?; Q13 = Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Table 2 presents the results of the critical appraisal for eligible quasi-experimental studies. Cause and effect was clear in all but one study. In five studies, Q2 and Q3 were not applicable because there were no comparisons made. There was no control group in nine of the 28 studies. Q7 was deemed not applicable to one study because no comparisons were made.

**Table 2: Critical appraisal results of eligible quasi-experimental studies**

| Citation | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 |
|---|---|---|---|---|---|---|---|---|---|
| Bouvette et al[73] | N | N | N | N | Y | Y | U | U | Y |
| Brilla et al[74] | Y | N/A | N/A | N | Y | Y | Y | Y | Y |
| Denq et al[75] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Elokda et al[76] | Y | Y | Y | Y | Y | N | Y | Y | Y |
| Faghri & Yount[77] | Y | Y | Y | Y | Y | N | Y | Y | Y |
| Gorelik et al[82] | Y | U | U | Y | Y | Y | Y | Y | Y |
| Gorelik et al[83] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Hamzaid et al[89] | Y | N/A | N/A | N | Y | Y | Y | Y | Y |
| Henry et al[51] | Y | N/A | N/A | N | N | U | Y | Y | U |
| Humm et al[52] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Kuznetsov et al[90] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Loew et al[70] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Lopes P et al[78] | Y | Y | U | Y | Y | Y | Y | Y | Y |
| Lucas RAI et al[91] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Mader SL.[79] | Y | Y | Y | Y | Y | Y | Y | Y | Y |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Puvi-Rajasingham & Mathias[53] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Rimaud, D. et al[68] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Shannon JR, et al[66] | Y | Y | Y | N | Y | Y | Y | Y | Y |
| Smit AAJ[56] | Y | Y | Y | N | Y | N/A | Y | Y | Y |
| Smit AA[57] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Ten Harkel et al[59] | Y | Y | Y | Y | Y | Y | Y | N | Y |
| Ten Harkel et al[58] | Y | Y | U | N | Y | Y | Y | Y | Y |
| Tutaj et al[93] | Y | N/A | N/A | N | N | Y | Y | Y | Y |
| van Lieshout et al[60] | Y | Y | N | Y | Y | Y | Y | U | Y |
| Wadsworth et al[92] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Yoshida et al[85] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Young & Mathias[54] | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Zion et al[80] | Y | N/A | N/A | N | Y | Y | N/A | Y | Y |
| **%** | **94.12** | **79.41** | **64.71** | **61.76** | **94.12** | **79.41** | **94.12** | **88.24** | **97.10** |

Y = Yes, N = No, U = Unclear, N/A – not applicable; JBI critical appraisal checklist for quasi-experimental studies; Q1 = Is it clear in the study what is the 'cause' and what is the 'effect' (i.e., there is no confusion about which variable comes first)?; Q2 = Were the participants included in any comparisons similar?; Q3 = Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?; Q4 = Was there a control group?; Q5 = Were there multiple measurements of the outcome both pre and post the intervention/exposure?; Q6 = Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?; Q7 = Were the outcomes of participants included in any comparisons measured in the same way?; Q8 = Were outcomes measured in a reliable way?; Q9 = Was appropriate statistical analysis used?

Table 3 presents the critical appraisal results for the eligible case report study. The intervention was not clearly described but all other aspects of methodological quality were reported.

**Table 3: Critical appraisal results of eligible case report**

| Citation | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 |
|---|---|---|---|---|---|---|---|---|
| Helmi[61] | Y | Y | Y | Y | N | Y | Y | Y |
| % | 100.0 | 33.33 | 100.0 | 66.66 | 66.66 | 100.0 | 66.66 | 100.0 |

Y = Yes, N = No, U = Unclear; JBI critical appraisal checklist for case report studies; Q1 = Were patient's demographic characteristics clearly described?; Q2 = Was the patient's history clearly described and presented as a timeline?' Q3 = Was the current clinical condition of the patient on presentation clearly described?; Q4 = Were diagnostic tests or assessment methods and the results clearly described?; Q5 = Was the intervention(s) or treatment procedure(s) clearly described?; Q6 = Was the post-intervention clinical condition clearly described?; Q7 = Were adverse events (harms) or unanticipated events identified and described?; Q8 = Does the case report provide takeaway lessons?

Confounding factors were not identified and not strategy to deal with confounding factors in the case control study. All other aspects of methodological quality were met as presented in Table 4.

**Table 4: Critical appraisal results of eligible case control study**

| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Galizia et al[62] | Y | Y | Y | Y | Y | N | N | Y | Y | Y |
| **Total %** | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 0.0 | 0.0 | 100.0 | 100.0 | 100.0 |

Y = Yes, N = No, U = Unclear; JBI critical appraisal checklist for case control study; Q1 = Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?; Q2 =Were cases and controls matched appropriately?; Q3 = Were the same criteria used for identification of cases and controls?; Q4 = Was exposure measured in a standard, valid and reliable way?; Q5 = Was exposure measured in the same way for cases and controls?; Q6 = Were confounding factors identified?; Q7 = Were strategies to deal with confounding factors stated?; Q8 = Were outcomes assessed in a standard, valid and reliable way for cases and controls?; Q9 = Was the exposure period of interest long enough to be meaningful?; Q10 = Was appropriate statistical analysis used?

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